COGNITIVE CONTROL IN VISUAL NEGLECT

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Abstract

Flexible behaviour in humans requires rapid choices between conflicting actions plans. Although much attention has focused on how prefrontal cortex guides action under situations of response conflict, little is understood about the contribution of parietal cortex. In this thesis I explore the role of the parietal lobe when action selection requires resolution of competition between conflicting motor programs.

Competitive imbalance between motor programs, resulting in disparity between leftward and rightward action plans, could in theory lead to directional motor bias in patients with parietal damage and spatial neglect.

The first three chapters reporting experimental findings examine directional motor performance in right-hemisphere stroke patients, with and without neglect. Using a modified Eriksen flanker task, we show that right parietal damage associated with leftward spatial neglect leads to paradoxical *facilitation* (speeding) of rightward movements in the presence of conflicting leftward response plans. These findings indicate a critical role for parietal regions in action planning when there is response competition. In contrast, patients with prefrontal damage have an augmented *cost* of conflict for both leftward and rightward movements. Subsequently, results from both masked prime and free choice tasks support a parietal role in directional motor processing.

Two further chapters reporting experimental findings investigate firstly the asymmetric basis of motor programming in normal subjects and secondly motor neglect, showing that underutilization of the left arm is associated with failure to suppress unwanted right-sided action plans.

Overall, the data presented in this thesis suggest that parietal cortex plays a key role in directional movement selection particularly when there is competition between potential action choices. Further, there is evidence for at least two independent systems, with right parietal cortex being a crucial site for automatic activation of competing motor plans and prefrontal regions acting in parallel to inhibit information irrelevant to current task goals.

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Chapter 1: General Introduction

In this thesis I explore a novel concept relating to the role of competition between motor programs in action selection. I propose that competing responses are propagated within parietal cortex and that an imbalance in response competition may result in directional motor deficits in patients with neglect following posterior parietal damage.

1.1 Getting the hand on target: the role of posterior parietal cortex

To understand the development of my hypothesis, it is first important to consider, in brief, evidence for a motor role of posterior parietal cortex. For convenience, I consider aspects of motor control serially but in reality, of course, brain computations are likely to run in parallel.

1.1.1 *Target selection and localisation*

Initial stages of motor planning require the subject to select a target. Posterior parietal cortex (PPC) is considered to play a major role in representing targets for action, as well as for perception (Gottlieb 2001). While only one potential target exists, selection on the basis of 'bottom-up' visual salience of the object may be suitable. However, when more than one potential target exists, *competition* is thought to occur both at a sensory level and *between action plans* to different target locations leading to a small delay in movement initiation (Eriksen and Eriksen 1974; Hodges, Lyons et al. 1997; Walker, Mannan et al. 2000). In this case, 'top-down' influence from behavioural goals and expectations of rewards may bias the outcome of such competition. In keeping with a role in action selection even when potential responses compete, representations in the PPC appear to be driven not only by stimulus salience

(Gottlieb, Kusunoki et al. 1998; Constantinidis and Steinmetz 2001), but also by task relevance and context (Gottlieb, Kusunoki et al. 1998; Stoet and Snyder 2004; Stoet and Snyder 2007) and probability of rewards (Platt and Glimcher 1999; Sugrue, Corrado et al. 2004; Sugrue, Corrado et al. 2005; Yang and Shadlen 2007).

The importance of PPC in choosing between competing potential targets was illustrated recently by Yang and Shadlen who showed that neurons within parietal cortex actually represented accumulating probabilities that underlie decision making processes (Yang and Shadlen 2007). They trained two monkeys to associate a set of ten shapes with varying likelihood of reward in a given direction (**Fig 1.1a**). At the end of the trial, the monkeys had to saccade to a target that was either within or outside its receptive field. The activity within individual neurons in the lateral intraparietal area (LIP) and the population as a whole clearly reflected the accumulating weight of evidence in favour of either a movement into or out of its receptive field (**Fig 1.1b**). In other words, these neurons apparently carried signals related to the most profitable reward outcomes for the animal.

Could the neuronal activity reflect the upcoming movement decision made by the monkeys, rather than the pure probabilities conferred by the shapes? The investigators attempted to dissociate pure probabilistic activity from the likelihood of making a movement in a given direction by subtracting the mean firing rate in each direction from the overall activity. They showed the

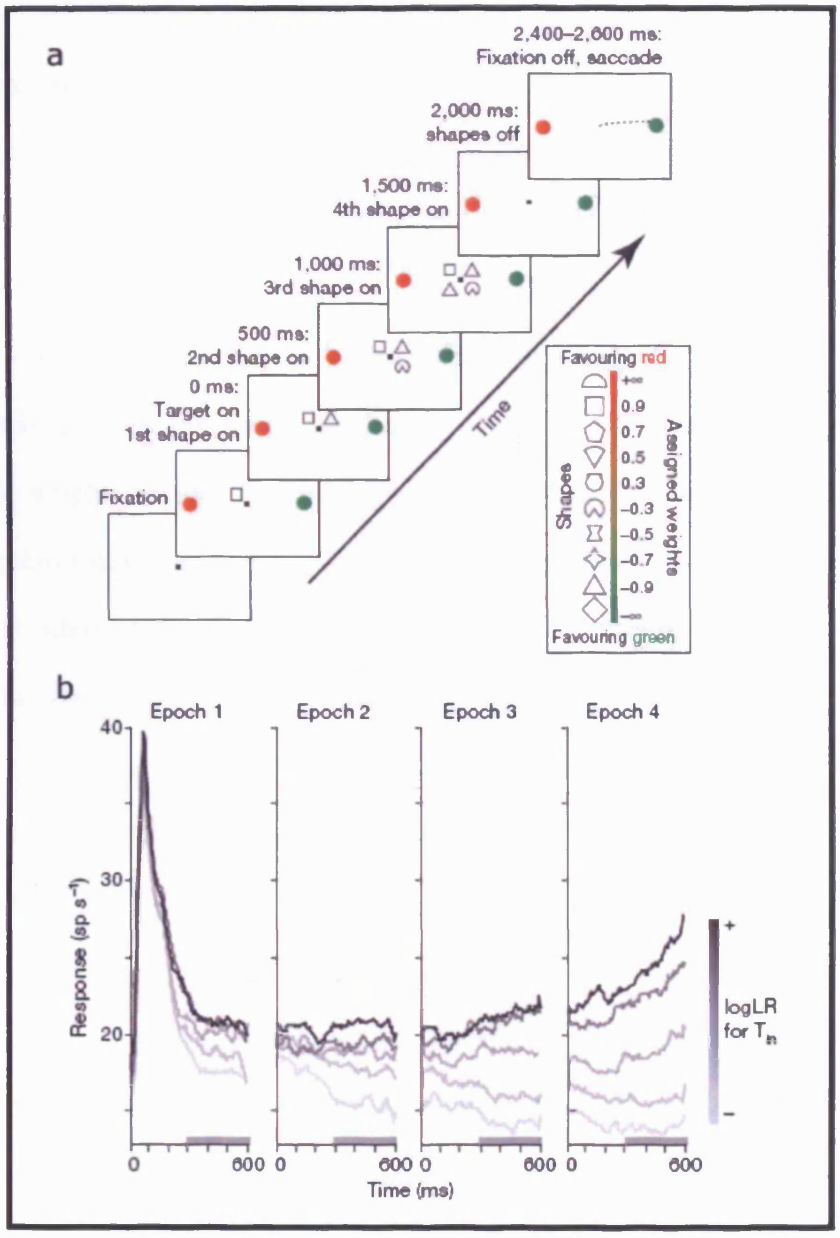


Fig 1.1 Task and population data from Yang and Shadlen 2007
a) Four shapes were presented sequentially on the computer monitor near the centre of gaze. After a brief delay period, the monkey made an eye movement (saccade) to either the red or green choice target. During neural recording, one of the choice targets was in the response field of the neuron. The shapes were selected randomly in each trial from a larger set of ten (inset). The reward was determined probabilistically by summing the weights associated with the four shapes. The sum is the logarithm of the odds that the red target will be the one rewarded which is similar to the cumulative assigned weights of the shapes (inset) after each shape is shown. Activity in individual neurons and the whole population (b) reflected the changing weight of evidence (log LR) as each shape was shown. The curves distinguished by different shades of grey represent average neuronal activity divided into 5 quintiles according to the probability associated with the preceding shapes, i.e. the black curve represents average neuronal firing patterns following shape combinations with a very high probability that an upcoming movement into the neuron's receptive field will be rewarded.

probabilistic modulation of firing rate persisted which they propose as evidence that rather than coding the direction of upcoming movement, these cells were purely responding to the probability of reward associated with the shapes.

However, subtraction of mean firing rate may not actually control for probabilistic changes in response decision which would be very closely related to the weight of evidence associated with the shapes. In fact dissociating the probability of reward from that of the upcoming movement decision is perhaps not possible using their paradigm. If neurons in PPC guide behaviour, one might expect them to modify response choice rather than just representing the sum of probabilities. In summary, PPC neurons appear to represent underlying probabilistic decision processes that are likely to modulate target and action selection.

A second critical aspect of visually-guided action is the ability to localise the target accurately. Such localisation may initially be in eye-centred coordinates but eventually requires transformation of target location to accurate motor commands in an effector-centred coordinate frame. Recent findings suggest that targets for action may be represented within parts of the PPC in a common eye-centred frame of reference (Buneo, Jarvis et al. 2002). Moreover, the PPC has often been considered to play a key role in sensorimotor transformations (Andersen and Buneo 2002; Battaglia-Mayer, Caminiti et al. 2003; Galletti, Kutz et al. 2003). Other studies, in awake-behaving monkeys and patients have implicated the PPC in updating target locations across eye or limb movements (Duhamel, Colby et al. 1992; Heide, Blankenburg et al. 1995; Duhamel,

Bremmer et al. 1997; Khan, Pisella et al. 2005). More recent investigations using functional imaging in humans have also revealed a role for the PPC in *remapping* target locations across saccades (Medendorp, Smith et al. 2002; Medendorp, Goltz et al. 2003; Merriam, Genovese et al. 2003). Thus, as well as a role in target *selection*, the PPC appears to play a significant part in target *localisation* and updating spatial locations across eye or limb movements.

1.1.2 *Issuing a motor command*

Once the target is localised, a motor command needs to be issued taking into account the difference between the current position of the hand and the location of the target – sometimes referred to as computation of 'motor error' (Buneo and Andersen 2006). At the highest level, such a command may still be in eye-centred co-ordinates (Buneo, Jarvis et al. 2002). Later, it would of course need to be converted to signals driving the appropriate motor neurones.

A motor role for PPC has been highly controversial (Andersen 1995; Colby and Duhamel 1996; Colby 1998; Batista, Buneo et al. 1999; Colby and Goldberg 1999; Andersen and Buneo 2002; Bisley and Goldberg 2003; Cui and Andersen 2007) with some authors suggesting that, rather than any intentional coding, the PPC has an attentional role (Colby and Duhamel 1996; Colby and Goldberg 1999; Goldberg, Bisley et al. 2002; Bisley and Goldberg 2003). Activity that codes motor intention within PPC has been shown in several studies (Andersen 1995; Bracewell, Mazzoni et al. 1996; Snyder, Batista et al. 1997; Batista, Buneo et al. 1999; Andersen and Buneo 2002). Snyder and colleagues (Snyder, Batista et al. 1997) found neurons in PPC that

were relatively more active in blocks where arm movements were required and other neurons that were selectively active when planning eye movements. Attentional and sensory requirements were the same regardless of the effector. Such effector-specific motor activity in PPC suggests an intentional role for this region. Of note, neurons in slightly different areas coded eye and hand movements; *inferior* LIP neurons were particularly sensitive to eye movement and more *superior* areas were associated with arm movements, leading to the naming of this area as the parietal reach region (see human analogue **Fig 1.2** - PRR).

Recently Cui and Anderson tested monkeys on a paradigm where they were always instructed in which direction to move from a central start position, but on 50% of the trials, monkeys were free to choose whether to move their eyes or hands to the target (Cui and Andersen 2007). A reward algorithm and intermingling of instructed with the free choice trials ensured that effector choice was well balanced. Even with these identical stimulus configurations, when monkeys chose to move their *eyes* in either direction, neurons in LIP were selectively active, whereas when *hand movements* were planned, activity was most marked in the PRR.

Despite such evidence for the involvement of the PPC in action selection and motor intention, some investigators attribute neuronal activity in PPC entirely to spatial attentional representation in multiple frames of reference (Colby and Duhamel 1996; Colby 1998; Colby and Goldberg 1999; Bisley and Goldberg 2003). They argue that effector-specific activation in LIP occurs because

saccade targets have a higher attentional priority than reach targets. However this does not explain the increased activity of cells in PRR when a reach is required (Scherberger and Andersen 2007), unless one assumes that multiple attentional representations in different brain areas selectively prioritise visual signals according to the effector with which they are associated, for example, LIP mediates attention for eye move movements and PRR attention for arm movements (Bisley and Goldberg 2003).

In addition, Bisley and Goldberg show that LIP neurons are more active following a signal to abort (NOGO), than carry out (GO) a response plan (Bisley and Goldberg 2003). They suggest that this is consistent with NOGO signals receiving a higher degree of attention than GO signals and therefore, LIP having a pure attentional role. However, NOGO signals require inhibition of a planned response which could be considered as alteration in the competitive bias between response choices.

Overall, my view is that data from neurophysiological studies of monkey PPC during response selection are in keeping with a motor role of PPC, although neurons with LIP are also modulated by attentional factors.

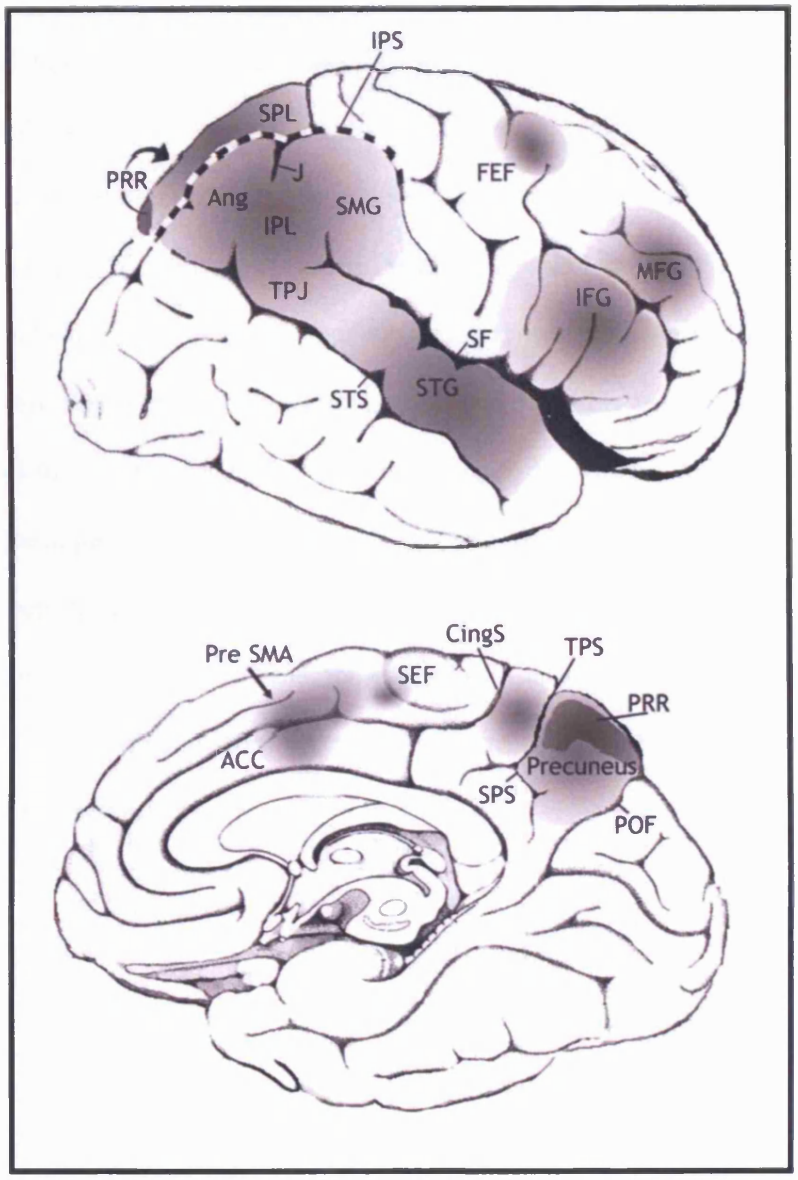


Fig 1.2 Cortical brain regions associated with visual neglect, motor and cognitive control

Neglect has been associated with damage in the inferior parietal lobe (IPL, comprising the angular gyrus (Ang) and supramarginal gyrus (SMG)), temporoparietal junction (TPJ), superior temporal gyrus (STG – bounded inferiorly by the superior temporal sulcus (STS) and superiorly by the sylvian fissure (SF)) and the inferior frontal gyrus (IFG). Damage to the superior parietal lobe (SPL) can result in optic ataxia and reaching related activity in functional imaging studies has been found in the intraparietal sulcus (IPS) and more medial parietal regions including the precuneus, particularly the parietal reach region (PRR). Posterior parietal cortex (PPC not shown) encompasses IPL and SPL.

Putative regions involved in processing response competition include the anterior cingulate cortex (ACC), pre-supplementary motor areas (Pre-SMA), supplementary eye fields (SEF) and the frontal eye fields (FEF) as well as IFG, middle frontal gyrus (MFG), IPL and SPL. Other relevant anatomical landmarks include the cingulate sulcus (CingS), sub-parietal sulcus (SPS), transverse parietal sulcus (TPS) and the parieto-occipital fissure (POF)

1.1.3 *Updating motor programs*

Simply issuing a command to move the limb in the correct direction, even after computation of motor error, would be insufficient alone to reach appropriately for a target. The kinematic profile (spatiotemporal characteristics such as spatial path, velocity and acceleration) of the reach will be affected by both perceived properties of the target and the aim of the movement (Marteniuk, Mackenzie et al. 1987). For example, reaching for a cup of tea will be affected by the apparent volume of liquid in the cup and whether the intention is to pick the cup straight up or first touch it to gauge its temperature. Even after these factors have been considered, the execution of an accurate reach requires the implementation of control systems that can monitor and modify the movement as it is performed.

To monitor the performance of a reach the brain needs to have predicted the consequences of its motor commands prior to their execution (i.e. it needs to compute ahead the behaviour of the arm, given a particular motor command). Such motor prediction is considered to depend upon 'forward models' of the motor system within the brain (Wolpert 1997; Desmurget and Grafton 2000). In addition, visual and somatosensory (including proprioceptive) feedback signals need to be integrated with copies of ongoing motor commands (efference copies), as well as knowledge about limb dynamics and visual feedback of the hand, to produce an estimation of the current state of the limb as the movement unfolds so that changes or corrections can be performed on-line (Desmurget and Grafton 2000; Wolpert and Ghahramani 2000). Finally,

the properties of the reach (e.g. direction, trajectory and temporal dynamics) need to be coordinated with those of the grasp (e.g. aperture, force, etc).

Lesion and transcranial magnetic stimulation studies in humans (Wolpert, Goodbody et al. 1998; Desmurget, Epstein et al. 1999; Pisella, Grea et al. 2000; Glover, Miall et al. 2005; Tunik, Frey et al. 2005) have provided evidence for an active role of the PPC in the *on-line* control of reaching and grasping, for example, when target location or size was altered during the course of the movement. Moreover, different regions within the human and monkey PPC appear to play differential roles in directing the reach and controlling grasp (Rizzolatti and Luppino 2001; Battaglia-Mayer, Caminiti et al. 2003; Connolly, Andersen et al. 2003; Culham, Danckert et al. 2003; Galletti, Kutz et al. 2003). For example, imaging studies have revealed a potential analogue of the monkey Parietal Reach Region or PRR (**see Fig. 1.2**) in the human precuneus on the medial surface of the superior parietal lobe (SPL), which is activated by reaching movements (Connolly, Andersen et al. 2003) while part of the anterior intraparietal sulcus is activated more by grasping in monkeys and humans (Culham, Danckert et al. 2003; Grefkes and Fink 2005). However, it remains unclear whether the PPC has a role in coordinating these two components during a reach.

Thus the evidence to date suggests that the PPC may play a critical role in several areas of visuomotor control, from target, and perhaps action, selection right through to on-line control during movement. The PPC has rich connections, via white matter tracts, to premotor regions in the frontal lobe,

cerebellum and basal ganglia consistent with a role in movement planning (e.g. (Stein and Glickstein 1992; Rizzolatti and Luppino 2001).

1.1.4 *Response competition*

The PPC has both the connectivity and neuronal properties to be involved in *response competition*. One study has even demonstrated directionally-tuned PPC neurons with task-specific delay in activity when responses compete (Stoet and Snyder 2007).

Stoet and Snyder trained two monkeys to respond with either a left or a right reach (Stoet and Snyder 2007, **Fig. 1.3**). On some trials, monkeys responded according to the colour of the imperative cue and on others, they responded to the orientation of the stimulus. In congruent trials, both colour and orientation had the same response association, i.e. cued movement in the same direction, whereas, in incongruent trials, different responses were associated with each of these features. The monkeys were slower to respond in the incongruent than congruent trials. Some PPC neurons were tuned both to the direction of movement and the relevant task dimension (colour or orientation) and these neurons had the greatest delay in reaching their half-maximum activity following an incongruent trial, compared to a congruent trial (**Fig 1.3c**). In fact, this delay is actually greater than the behavioural incongruence delay shown by the monkey (**Fig 1.3 b,c**).

Such PPC neurons suggest an important role for task-sensitive neurons in converting sensory signals to motor commands particular when responses

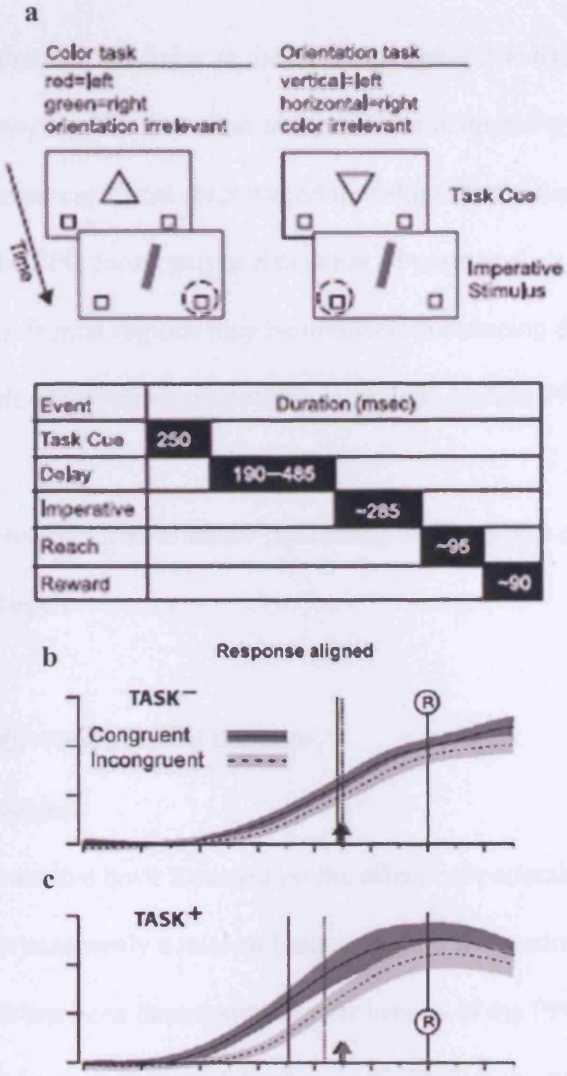


Fig 1.3 Paradigm and neurophysiological results from Snyder and Stoet 2007

Trials of two tasks were interleaved (a). In the colour and orientation tasks, monkeys responded to the colour and orientation of the imperative stimulus respectively by reaching to one of the two white squares on the left and right side of the screen. In congruent trials, both orientation and colour were associated with the same direction of reach, whereas in incongruent trials, colour and orientation had different response associations.

Lower panels (b,c) shows onset of neural directional response (preferred minus nonpreferred direction) as a function of task selectivity and imperative stimulus congruency. Vertical black solid bar is the time to half maximum activity for congruent trials and vertical dashed line is for incongruent trials. Black and grey arrows indicate average saccade latencies in the congruent and incongruent condition respectively. Neurons with the greatest delay to reach half-maximum activity in the incongruent condition, compared to the congruent, were task sensitive. This delay shown in (c) – 32 ms – was greater than the behavioural incongruent delay shown by the monkey (earliest motor response saccade latency is 15ms).

compete. The fact that the delay in the PPC neurons is greater than the behavioural delay implies that other brain areas or neuronal types must also be involved in processing signal response relationships that underlie response selection. So the PPC forms part of a network of areas and, as we discuss later (in **section 1.4**), frontal regions may be involved in reducing delays that might occur as a result of response competition in regions such as PPC.

Next we ask what happens to motor processing and response competition when the PPC is damaged.

1.2 Deficits following parietal damage

1.2.1 *Monkey lesions*

Relatively few studies have focussed on the effects of parietal lesions in monkeys. Most commonly a misreaching deficit for the contralateral *arm* in both hemifields has been demonstrated after lesions of the PPC (Hartje and Ettlinger 1973; Faugier-Grimaud, Frenois et al. 1978; Lamotte and Acuna 1978; Faugier-Grimaud, Frenois et al. 1985). This at first appears to contrast with deficits in human reach patterns following PPC damage which tend to be worst in the *contralateral side of space* using either arm ((De Renzi 1982) and see **section 1.2.2** for a full discussion).

While these differing results could imply that monkey and human PPC have different functions, further work has suggested that the precise area of PPC damaged critically alters the reaching deficit. By cooling areas of PPC to cause inactivation, Stein showed that lesions of the superior parietal lobule produced

misreaching of the contralateral arm in all directions (Stein 1978). In contrast, cooling of the inferior parietal lobe leads to misreaching with both arms in the contralateral field. Therefore subregions within PPC are likely to be important for different aspects of reaching.

1.2.2 *Neglect – common sequela to PPC damage in humans*

Damage to the right parietal lobe of humans often results in neglect (Mort, Malhotra et al. 2003). Hemispatial neglect affects up to two thirds of acute right hemisphere stroke patients and is associated with poor prognosis (Stone, Halligan et al. 1993; Buxbaum, Ferraro et al. 2004). Patients with neglect fail to orient themselves to stimuli on the contralesional side of space and preferentially attend to ipsilesional objects (Brain 1941). Bedside clinical tests for neglect reflect lateralised bias, for example, patients with right hemisphere stroke omit left-sided objects when performing cancellation tasks, such as the Bells test (Gauthier, Dehaut et al. 1989) and bisect a horizontal line (Wilson, Cockburn et al. 1987) towards the right rather than at the centre (**Fig 1.4**). However, abnormal performance on these clinical tests does not reveal the cause of the lateral bias which could result from either single or combinations of underlying component deficits (Husain and Rorden 2003; Hillis 2006; Coulthard, Parton et al. 2007).

Left visual neglect has been documented to result from damage in several different brain regions (**Fig 1.2**) including right inferior parietal (Vallar and Perani 1986; Mort, Malhotra et al. 2003), inferior frontal (Husain and Kennard 1997), superior and medial temporal (Mort, Malhotra et al. 2003; Karnath,

Fruhmann Berger et al. 2004) cortices as well as subcortical regions such as basal ganglia and thalamus (Vallar and Perani 1986; Karnath, Himmelbach et al. 2002). Patients with lesions in these different places all have a rightward bias, but underlying component deficits would be expected to differ according to each patient's specific area of brain damage (Coulthard, Parton et al. 2007). Although the nature of underlying component deficits associated with different lesion locations is not yet fully known, neglect research has revealed behavioural dissociations within groups of patients suggesting that the syndrome is heterogeneous (**Fig 1.5** - Husain and Kennard 1997 ; Mattingley and Driver 1997; Husain, Mattingley et al. 2000; Malhotra, Mannan et al. 2004).

Cognitive impairments found in patients with neglect include pathological perceptual, attentional or representational asymmetries all of which could account for bias towards the right side in patients with right brain damage (Bisiach and Luzzatti 1978; Heilman and Vandenabell 1980; Mesulam 1981). While much focus has been on sensory and attentional component deficits of the neglect syndrome, abnormal *motor* processing has also been shown (Mattingley, Bradshaw et al. 1992; Behrmann and Meegan 1998; Mattingley, Corben et al. 1998; Husain, Mattingley et al. 2000; Behrmann, Ghiselli-Crippa et al. 2001).

Putative motor deficits in neglect can be divided into two broad categories. The first affects the ipsilateral, relatively intact arm; the right arm in those

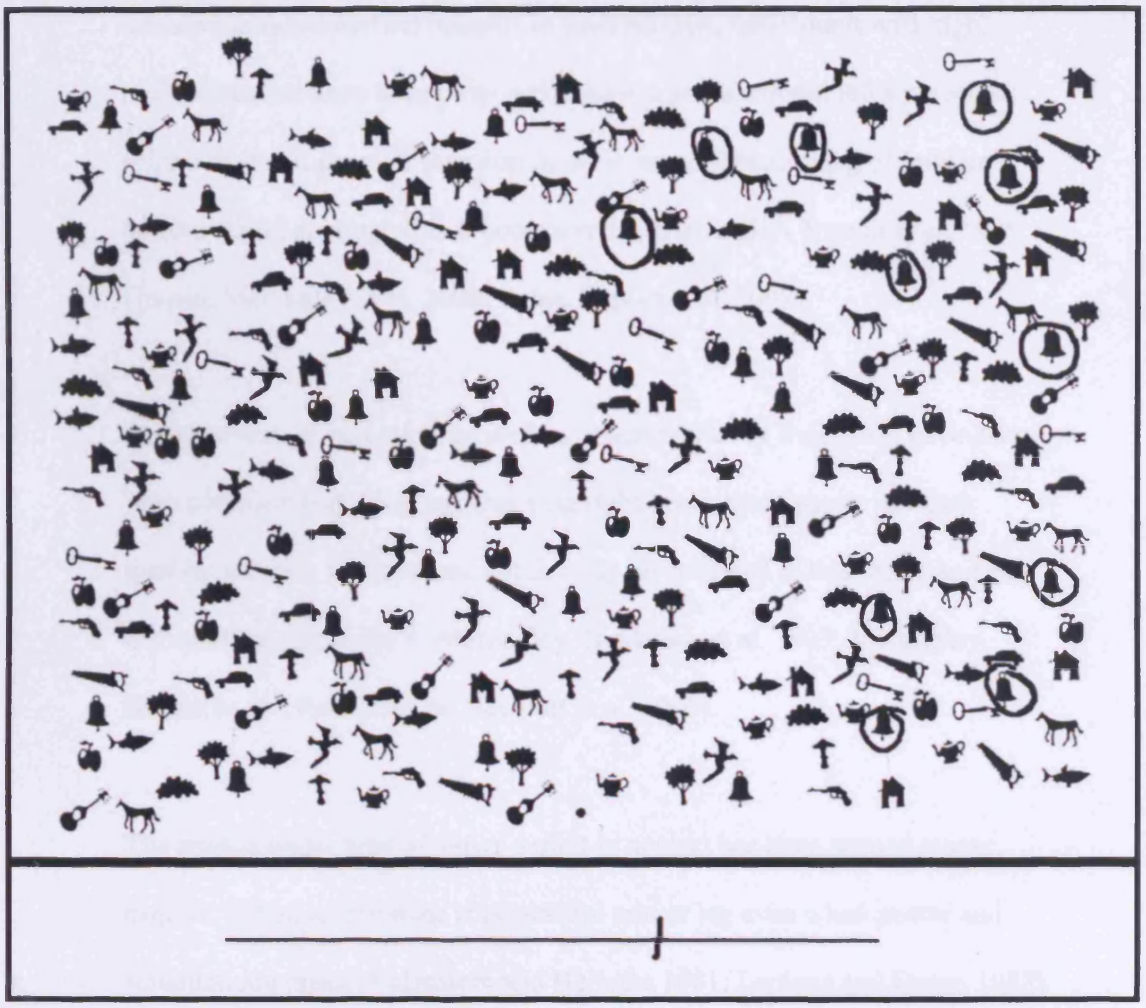


Fig 1.4 Bells cancellation and line bisection task
Patients with left neglect tend to mark objects on the right of the page. This lateralised bias is exacerbated when the scene is cluttered as shown above. Neglect patients also bisect a 17cm long line towards the right of the true midline as shown.

with right hemisphere stroke. *Directional hypokinesia* describes slowness to initiate contralesional movements in such patients. Individuals with right parietal neglect have been proposed to have true directional leftward motor *initiation* slowing, rather than just delay in sensory processing of leftward target stimuli, although this is controversial (Mattingley, Husain et al. 1998; Husain, Mattingley et al. 2000; Sapir, Kaplan et al. 2007).

Slow movement execution, as well as abnormalities of trajectory, have also been demonstrated when patients with right hemisphere stroke use their ipsilesional arm, but these are not directly investigated in this thesis and are discussed in **Appendix 1** (Mattingley, Bradshaw et al. 1992; Mattingley, Husain et al. 1998; Jackson, Newport et al. 2000).

The second major type of motor deficit in neglect has been termed *motor neglect*, failure to move the contralateral arm or leg even when power and sensation are intact (Valenstein and Heilman 1981; Laplane and Degos 1983). Although extremely common following stroke (Siekierka-Kleiser, Kleiser et al. 2006) relatively little work has focussed on the abnormalities of motor processing that actually underlie motor neglect. Even diagnosis of the syndrome can be difficult as it often co-exists with hemiparesis and visual neglect (Punt and Riddoch 2006). Recent work has suggested that alterations in the competitive balance in motor planning between the two arms may accompany motor neglect (Punt, Riddoch et al. 2005; Punt, Riddoch et al. 2005).

Next motor initiation deficits in the neglect syndrome are discussed in detail, and then the evidence that such movement abnormalities actually reflect deficits in motor planning rather than sensory processing is reviewed.

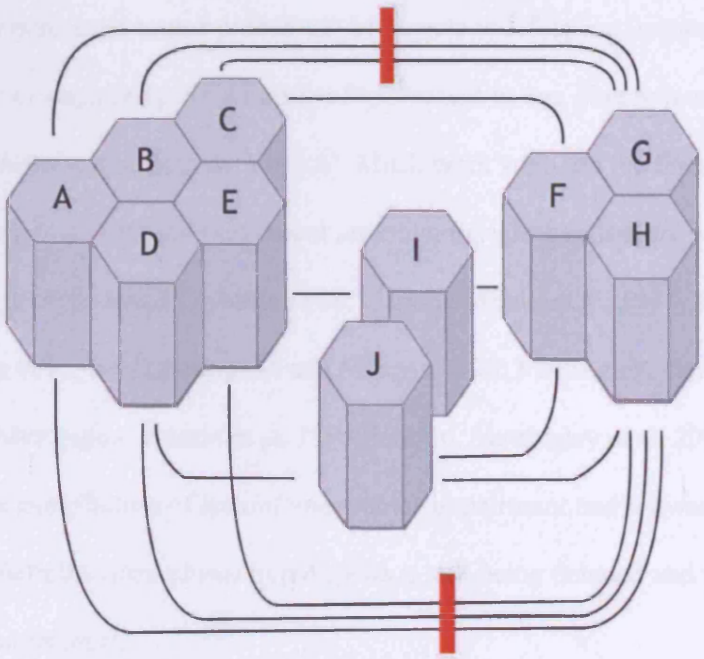


Fig 1.5 Modular architecture of the neglect syndrome.
Neglect may emerge from damage to a combination of cognitive and visuomotor control modules, labelled A-J for illustrative purposes here. These modules are present in anatomically distant regions, for example, in parietal, frontal and subcortical regions. Stroke lesions may damage different combinations of critical modules in different neglect patients. None of the deficits that might arise from damage to a module need be specific to the neglect syndrome, but when critically combined, they may lead to the behavioural syndrome we classify as neglect. Even small lesions in white matter connections (marked in red) between these modules may suffice to disconnect or lead to widespread disruption within this architecture.

1.2.2.1 *Neglect patients slow to initiate action*

Directional hypokinesia (DH) describes the slowing of movement initiation towards the contralesional side in patients with unilateral brain injury (Heilman, Bowers et al. 1985; Harvey, Milner et al. 1994; Mattingley, Husain et al. 1998; Husain, Mattingley et al. 2000). In theory, this could be caused either by slowed perceptuo-motor processing of objects in left space (*spatial* visuomotor deficit) or impaired programming of movement in one direction only (*directional* motor deficit - **Fig 1.6**). Much work supports the finding of an impairment of leftward movement initiation in right-hemisphere patients with left neglect (Fisk and Goodale 1988; Harvey, Milner et al. 1994; Mattingley, Phillips et al. 1994; Behrmann and Meegan 1998; Mattingley, Corben et al. 1998; Mattingley, Husain et al. 1998; Husain, Mattingley et al. 2000). But, the relative contribution of *spatial* visuomotor impairment and leftward directional motor deficit to *directional* hypokinesia is still being debated and may differ between patients.

Heilman and colleagues tested right and left brain-damaged subjects on a task that required either leftward or rightward movements to be made along a fixed linear track (Heilman, Bowers et al. 1985). All right brain-damaged patients in this study had neglect and as a group they were slower to initiate movements leftward than rightward regardless of whether the track was placed in the right or left hemispace. Although this appears to be evidence in favour of a directional rather than spatial deficit, it is possible that patients visualized an end target in order to make the movement. So a relative left spatial deficit is still a possibility.

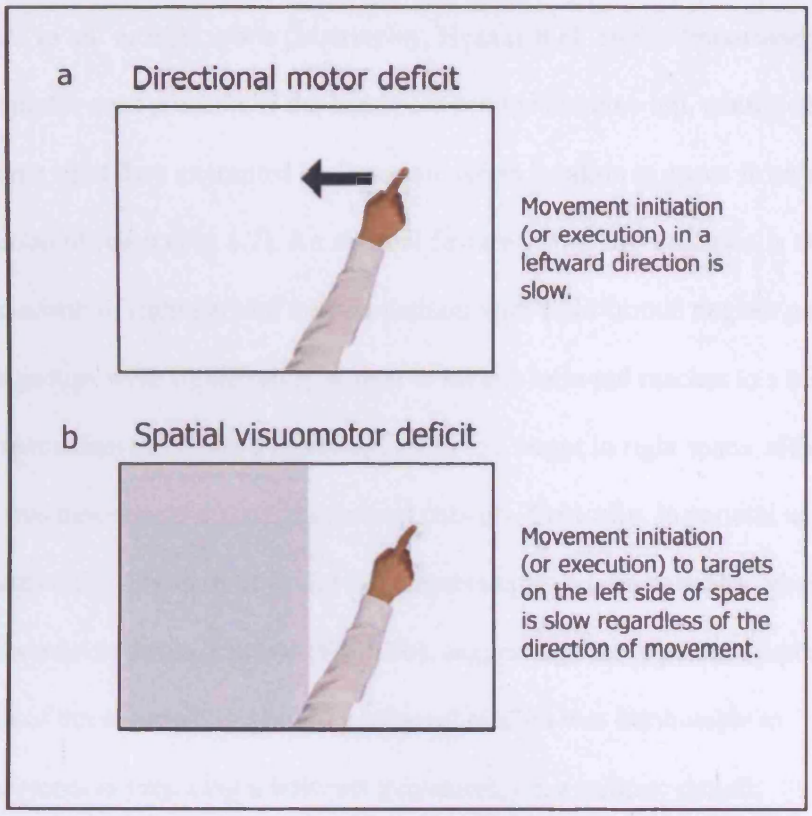


Fig 1.6 Directional motor verses spatial visuomotor deficits
Difficulties in reaching to a left target could be due to a directional motor deficit, i.e. in moving leftward (a). On the other hand, they might be due to moving the hand into left hemispace, regardless of the direction of movement (b). Examination of rightward reaches to targets in left hemispace is required to dissociate these alternatives.

Mattingley, Husain and colleagues studied leftward or rightward reaches to targets in left or right space (Mattingley, Husain et al. 1998). Importantly, by varying the start position of the hand between the extreme left, centre, or extreme right they attempted to dissociate target location in space from the direction of reach (**Fig 1.7**). An unusual feature of this investigation is the comparison of right parietal neglect patients with right frontal neglect patients. Both groups were significantly slower to initiate leftward reaches to a target in left space than to initiate a rightward reach to a target in right space, although this was more marked for right parietal patients. Critically, in parietal neglect patients only, initiation times for left targets improved dramatically when a rightward reach was required (**Fig 1.7b**), suggesting that in parietal patients much of the slowness in initiating leftward reaches was attributable to impairment in preparing a leftward movement, i.e. a motoric deficit.

The pattern of performance observed for **frontal neglect patients – those with lesions centring on the ventral premotor cortex – on the reaching task** was very different to that found in the parietal patients. Frontal neglect patients were slower to initiate reaches to a target in left hemispace regardless of whether the direction of the reach was leftwards or rightwards. Such a pattern of impairment in the frontal group is clearly not explained by a *directional* motor deficit but it might be attributed to a *spatial* visuomotor deficit (specifically in initiating movements to targets in left hemispace - **Fig 1.6**).

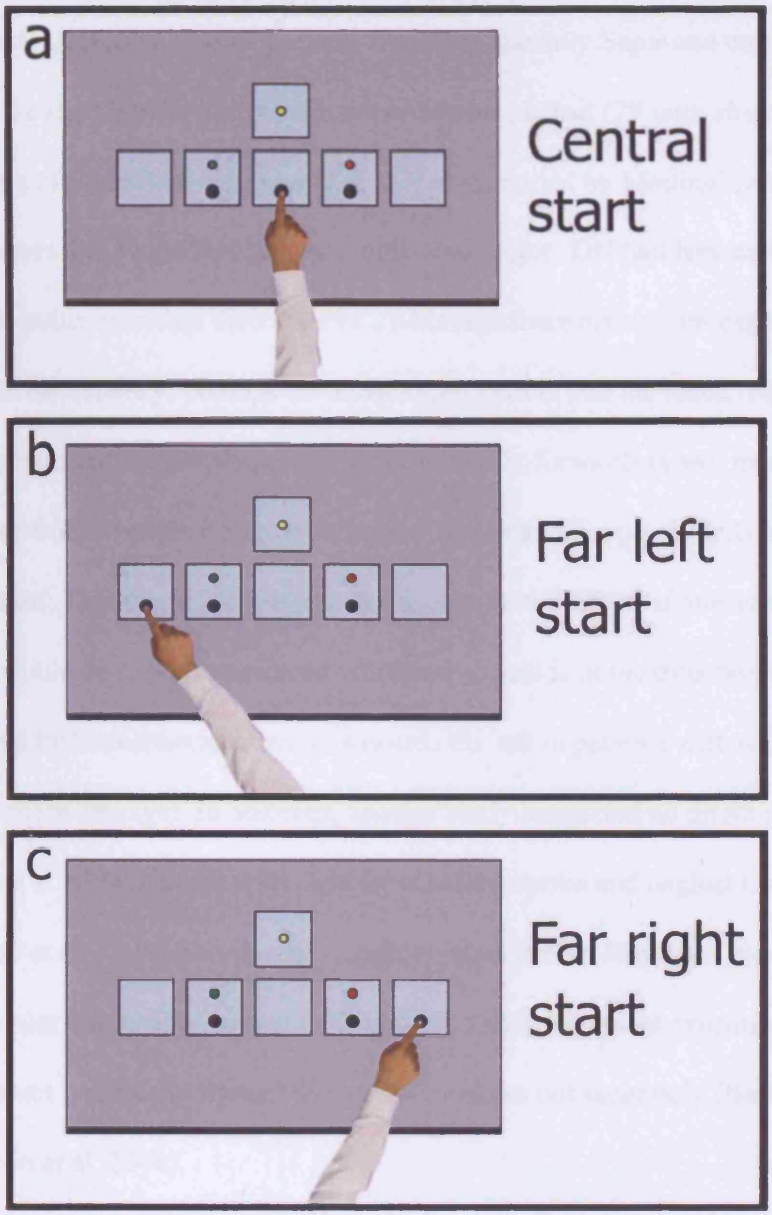


Fig 1.7 Apparatus used to dissociate movement direction from target location in the study by Mattingley and colleagues
Subjects fixated the central yellow light and moved to press a button under the green light (in this case illuminated in left hemispace). In some trials a red distractor was lit on the opposite side. The start position of the hand was varied as shown. Movement initiation time was measured using the time taken to release the button at the start position. In the control task (which did not require any directional movement), the subjects pressed the button at the start position as soon as they could after the illumination of the left or right targets.

A couple of studies challenge these findings. Recently Sapir and colleagues tested 52 right hemisphere stroke patients with neglect (29 with structural imaging available) on a similar task to that described by Mattingley and colleagues and found that patients with 'true motor' DH had lesions in the ventral putamen rather than the PPC. Although there are several explanations for this discrepancy, perhaps the most significant is that the reach required in their version of the paradigm was predominantly forwards (away from the patient) from a button box to a computer screen and not purely leftward or rightward. This might reduce any directional motor effects if one assumes that these would be most pronounced when movement is in the direction most affected by hemispheric damage (towards the left in patients with right hemisphere damage). In addition, another study suggested no directional slowing at all in patients with right hemisphere stroke and neglect (Bartolomeo, D'Erme et al. 1998; Bartolomeo, Chokron et al. 2001). However, reaction times in their paradigm consisted of both initiation and movement execution times, so it is not possible to dissect these two variables out separately (Bartolomeo, Chokron et al. 2001).

In the work described above, only patients with neglect were tested and therefore they do not reveal if DH is a neglect-specific deficit. In a different study, Mattingley and colleagues tested both left and right hemisphere stroke patients with or without neglect asking them to press buttons sequentially in a rightward or leftward direction (Mattingley, Bradshaw et al. 1992). Only patients with neglect had DH when performing this task. While it is difficult to prove that a component behavioural abnormality such as DH contributes to the

neglect syndrome, the finding that DH occurs mainly in patients with neglect is consistent with this argument.

Data presented so far relate to motoric deficits with the ipsilesional arm as very little work has focused on motor neglect of the contralesional arm. One study has investigated motor initiation slowing in a single right hemisphere patient with motor neglect of the left limb (Valenstein and Heilman 1981). Valenstein and Heilman show that even when stimuli were non-lateralised (vertically aligned), their motor neglect patient was slower to initiate movement with his left arm than the right especially when bilateral movements were required. So these patients appear to have a limb specific, non-spatial motor initiation deficit. Component factors that may contribute to motor neglect, such as this non-spatial motor initiation impairment, have received relatively little attention despite motor neglect complicating more than one third of stroke cases (Siekierka-Kleiser, Kleiser et al. 2006).

In summary, patients with neglect are slow to initiate contralesional movements (directional hypokinesia). Most studies of neglect have tended to group together patients according to clinical syndrome. However, this is likely to result in clustering patients who may behave strikingly differently due to different lesion locations and component deficits. Therefore, insight into both the neglect syndrome and cognitive processes adversely affected following stroke may be furthered by seeking lesion-behaviour correlations within groups of patients with and without neglect. One study has divided patients according to their lesion site and suggested that DH has a directional motor component

(worse for reaches to left-sided targets in a leftward direction only) in patients with isolated parietal lesions (Mattingley, Husain et al. 1998; Husain, Mattingley et al. 2000). In contrast, patients with frontal lesions may have a visuo-spatial basis for their DH, i.e. they are slow to perceptually process leftward target information which results in a slow reach (Mattingley, Husain et al. 1998; Husain, Mattingley et al. 2000).

The relative contributions of sensory and motor component deficits to the neglect syndrome are discussed in the next section.

1.2.2.3 *Reaching deficits in neglect: perceptual or motor?*

What causes the movement deficits observed in neglect patients? Many investigators have considered this problem from the perspective of perceptual vs motor impairments. The landmark task, which requires subjects to point to the end of a pre-transected line that they consider to be nearest to the transection, has been used widely as a tool to distinguish between motor and perceptual contributions in neglect (Bisiach, Geminiani et al. 1990; Milner, Harvey et al. 1993; Harvey, Milner et al. 1995; Bisiach, Ricci et al. 1998). It was proposed that if the subject has a perceptual distortion, the left half of a centrally bisected line will appear shorter and the subject will respond leftward. Conversely, if the subject has a motor bias, he will tend to point toward the right of the line regardless of the location of the transection.

The proportion of patients classified as having perceptual and/or premotor deficits varies between the different landmark tasks perhaps because of

variation in perceptual difficulty of these tasks: Harvey and colleagues (1995) required a perceptual judgement of lines prebisected at a maximum of 5mm from the centre whereas Bisiach and colleagues (1998) presented shorter lines with bisection points 30 to 150 mm from the centre. The latter demanded a much easier perceptual judgement and this could explain why they identified a higher proportion of people with a "premotor" deficit. Thus the landmark task reveals *predominant*, rather than exclusive, motor or sensory biases, especially when the motor bias may manifest as slowed rather than inaccurate movement.

Several other ingenious paradigms using, for example, pulleys or epidiascopes (Nico 1996; Harvey, Kramer-McCaffery et al. 2002) have also been used to dissociate the direction of hand movement from the perceived visual information. These tasks all require subjects to move a visual stimulus by making incongruent hand movements, i.e. in the opposite direction to the perceived visual stimulus (Coslett, Bowers et al. 1990; Tegner and Levander 1991; Harvey, Milner et al. 1995; Nico 1996; Bisiach, Ricci et al. 1998). Therefore, subjects with lesions that cause particular susceptibility to task incongruity, e.g. frontal patients, might be impaired on this type of task, regardless of whether they have a directional motor deficit (See Mattingley and Driver 1997 for a discussion). There is little consistency across these perception vs motor paradigms and the correspondence between deficits on these tasks and impairments in simple reaching is not obvious (Harvey, Kramer-McCaffery et al. 2002; Harvey 2004). Nevertheless, these studies do reveal dissociations between patients and, again, these may relate to differences in lesion location, although this has not been systematically investigated.

In other attempts to dissociate visuomotor deficits in neglect, investigators have looked at the effect of the intended purpose for which a movement is made on task performance. In one study patients with left-sided neglect were asked to point to the middle of a rod or to grasp it at the centre (Robertson, Nico et al. 1995). Patients reached well to the right of centre when pointing, but when required to grasp the rod, they reached closer to the centre. Different paradigms have revealed similar dissociations resulting in the claim that perhaps neglect patients have damage in areas of the visual system involved in perceptual judgement, but relatively spared the vision-for-action (dorsal) processing stream (Pritchard, Milner et al. 1997; McIntosh, McClements et al. 2004).

This finding is not consistent across all neglect patients with one study revealing that such a dissociation was lesion-dependent occurring only in a patient with occipito-temporal damage secondary to a posterior cerebral artery stroke, and not in two patients with occipito-parietal damage following middle cerebral artery stroke (Pritchard, Milner et al. 1997). In addition, no clear dissociation between spared vision-for-action and impaired vision-for-perception in neglect exists when neglect patients are tested using a paradigm in which perceptual and action conditions are carefully matched for difficulty (Marotta, McKeeff et al. 2003).

What about the movement initiation deficit observed in neglect patients? Many investigators have considered this also to be explained by dissociable

perceptual and motor deficits, which might even have separate anatomical bases. For example, Mesulam suggested that motor deficits in neglect result from frontal lesions whereas more posterior lesions involving the parietal cortex are associated with a predominantly perceptual variant of neglect (Mesulam 1981). In principle, both types of deficit – perceptual or motor – could lead to a motor initiation deficit.

The paradigm used by Mattingley, Husain and colleagues to dissociate direction of reach from target location (**Fig 1.7**) did reveal differences between neglect patients with parietal and frontal lesions (Mattingley, Husain et al. 1998; Husain, Mattingley et al. 2000). But *contrary* to the proposal first advanced by Mesulam (1981), it demonstrated that parietal neglect patients have a directional *motor* deficit. However, closer examination of the findings suggests that reach direction cannot be the only determinant of the parietal deficit.

In this paradigm, leftward reaches were made not only to the target on the left; they were also required to the target in right hemispace when the initial starting point of the hand was on the extreme right (see arm position in **Fig 1.7b**). But when such a leftward reach was required to a target on the right, there was no increased 'cost' in initiation time, compared to a rightward reach to the right target. Thus, the parietal deficit was actually modulated by both location of target in space and the direction of reach, with the impairment being evident only when a *leftward* reach was required to a target in *left hemi-space*. The deficit might therefore be better considered to be due to an interaction of a

sensory, localisation deficit with a difficulty in issuing a motor command for a leftward movement. These factors, together with visual deficits in neglect, may produce directional hypokinesia.

Therefore, it is possible that a simple perceptual vs motor distinction may not be helpful. Directional hypokinesia could, in theory, result from predominantly perceptual or motor deficits, but it could also just as well arise from intermediate processing stages, or even damage to representations that subserve both perception and action. Given that parietal cortex has been shown to have a role in sensory and motor functions as well as sensorimotor transformations (**section 1.1**), one would expect that deficits resulting from parietal damage would involve both sensory and motor systems.

Most of the data presented above relate to right hemisphere stroke. In this thesis, we investigate the possibility that the right PPC is involved in response competition and particularly allows leftward response plans to compete equally with right. But would we expect a similar role for the left PPC? In the next section, the relevance of hemispheric lateralisation of motor control to the neglect syndrome and response competition is discussed.

1.2.2.3 *Distinct motor control modules in each hemisphere.*

Are there equivalent, symmetrical deficits following right and left hemisphere stroke? Basic sensory and motor functions are represented contralaterally within the brain, for example, left hemisphere stroke results in right hemiparesis or sensory loss. However, there are well-accepted examples of

"higher order" functions for which one side of the brain is dominant (Brain 1941; Kimura and Archibald 1974; Heilman and Abell 1980; Kimura 1982). It has been argued that such hemispheric specialisation may have been evolutionarily beneficial as reduction in interhemispheric competition is perhaps more efficient for certain processes (Toga and Thompson 2003).

Visual neglect is more common and enduring following right than left hemisphere stroke (Stone, Wilson et al. 1991). One possible explanation for this is that right hemisphere is dominant for spatial attention or representation (Heilman and Abell 1980; Mesulam 1981; Pouget and Driver 2000), i.e. activity within the right hemisphere covers both the left and right sides of space and therefore can compensate for left hemisphere damage. However, the reverse does not occur as left hemisphere subserves a contralateral attentional function only. Consistent with such a role for the right hemisphere, functional imaging demonstrates a right-lateralised attentional network (Mesulam 1981; Corbetta and Shulman 2002).

It has also been proposed recently that neglect is particularly severe after right brain damage because of associated injury to right hemisphere regions involved in non-lateralised cognitive processes (Corbetta and Shulman 2002; Husain and Rorden 2003). In this case, the neglect behaviour manifest by an individual patient may be envisaged to be the result of damage to several brain areas each subserving an individual, modular function (**Fig 1.5**). While impairment of a module that results in a lateralised deficit may be essential for the presence of neglect, damage in other areas with non-lateralised functions may determine

the severity or longevity of neglect. For example, impairment of spatial memory, remembering the locations of objects on either side of space, is thought to interact with and perhaps exacerbate spatial bias, worsening the neglect syndrome (Malhotra, Parton et al. 2003; Malhotra, Mannan et al. 2004; Mannan, Mort et al. 2005; Ferber and Danckert 2006). Therefore, it is perhaps damage to several regions of right hemisphere with distinct functions that results in severe neglect. Moreover, the combination of impairments may differ across patients, accounting for the heterogeneity of the syndrome.

Left hemisphere stroke often results in dyspraxia, impairment of skilled actions, and speech disturbance (Kimura and Archibald 1974; Blank, Scott et al. 2002). Parallels between the fine motor skills required for speech and manual dexterity have led some authors to assert that the left hemisphere is dominant for motor control. Patients with left parietal lesions are impaired when single hand movements are required and those with left inferior frontal damage are slow to produce single syllables (Kimura 1982). Both groups (left parietal and frontal) fail to produce sequences of hand movement or speech sounds normally, suggesting perhaps that they have a generalised deficit at the level of motor selection.

If the left hemisphere is dominant for motor control, would we really expect any true motor deficits in patients with neglect following right hemisphere stroke? Studies investigating left hemisphere control of movement have employed a range of paradigms such as mimicking hand postures or repeatedly tapping fingers (Buxbaum, Kyle et al. 2006; Serrien, Ivry et al. 2006). While

the left hemisphere does appear to be important for these types of movements it is possible that the right hemisphere may be critical for motor control in other contexts. Evidence described above suggests a role for the right hemisphere in motor control, particularly in speeded responses with a leftward directional component (Mattingley, Husain et al. 1998; Husain, Mattingley et al. 2000; Sapir, Kaplan et al. 2007).

One study has investigated differential roles of right and left parietal lobe in motor control by comparing activity when both self-generated and externally generated motion are viewed and then one is occluded so a representation must be maintained (Ogawa and Inui 2007). The right parietal lobe more strongly activated when the *externally* triggered motion was occluded, whereas the left parietal lobe responded to occlusion of the *self-generated* activity. This suggests that the right parietal lobe may be important for visuomotor transformations required for guiding externally triggered movements whereas the left parietal lobe mediates internally generated movement.

Overall, there is evidence for motor processes occurring within human right and left PPC, although the nature of these is still far from fully understood. Could it be that patients with PPC damage and neglect are impaired at representing competing response programs and this underlies directional hypokinesia? Next, evidence for failure of response competition processing in patients with neglect is reviewed.

1.2.2.4 *Abnormal response competition in parietal lesions and neglect?*

Directional movements using either arm are disrupted by distracting stimuli in both healthy subjects and neglect patients. However, the pattern of interference differs between the two groups perhaps suggesting abnormalities of cognitive control in patients with neglect. In healthy individuals, right-sided distractors significantly slow movement with the right arm to left-sided targets – 35ms increment in reaction time (Hodges, Lyons et al. 1997). By contrast, movement of the left arm is susceptible to interference from distractors on *both* sides of space (43 ms increment with left sided distractors and 23 ms with right sided distractors). If one assumes that distractor effects in each arm reflect interference in processing within the contralateral hemisphere, these findings perhaps suggest a distinct role for the right hemisphere in the resolution of competition between potential targets across space.

The performance of individuals with right hemisphere damage in the presence of distractors reveals large deficits in the early stages of reaching consistent with increased susceptibility to interference during motor planning. For example, Behrman and Meegan (1998) found that neglect patients with right hemisphere lesions (both parietal and parieto-frontal) were highly susceptible to distraction on the right, with movement initiation times increasing by >200 ms (compare with normal distractor costs shown above). By contrast, there was no significant interference from leftward distractors. Importantly, these patients with neglect were also more likely to make errors in the direction of movement; when a target to the left was accompanied by a distractor to the right they were more likely to misreach towards the distractor.

In their study, Husain and colleagues (2000) found that right parietal neglect patients showed interference from distractors only when reaching from far left (161 ms increment) or central (68 ms) starting positions regardless of the position of the distractor. When the start position was far right (**Fig 1.7c**), the distractor was always to the left of the start position and therefore could effectively have acted as a second stimulus to boost leftward target selection and movement initiation.

To investigate further the stage of processing influenced by the presence of distractors, Mattingley et al. examined the distractor effect on movements to targets which appeared in locations that were either predictable or unpredictable (Mattingley, Corben et al. 1998). They found that ipsilateral distractors prolonged reaction times for contralesional movements, but only when the movement was unpredictable. Thus the distractor was only influential when there was more than one potential response, consistent with the view that the distractor effects occurred *only when there was competition between action choices.*

When patients choose between two possible button-press responses to a target and have to ignore distractors in one or other visual field, interfering contralesional stimuli tend to have less impact than ipsilesional ones on response times (Ro, Cohen et al. 1998; Snow and Mattingley 2006). However, contralesional distractors can delay response in patients with neglect even when sometimes the interfering stimulus is not reported by the patient (Cohen,

Irvy et al. 1995; Ro, Cohen et al. 1998). This implies that some response channels are activated in these patients in the absence of visual awareness. Ro and colleagues suggested that contralesional interference was most marked in patients without damage to the temporoparietal junction (Ro, Cohen et al. 1998). Patients with temporoparietal damage showed very little effect of incongruent information from the contralesional side.

While the above studies suggest that patients with neglect are abnormally susceptible to distraction while planning movements, it is critical to consider the nature of the distraction. The distractors were different coloured lights from the target on either side of space and could have interfered with the selection of a target for action at several levels of visuomotor processing including perceptual, attentional and motor. The potential *motor* program activated by a distractor was entirely dependent on its spatial location.

Here, we are interested in whether patients with neglect process competing directional *motor* programs normally. In order to dissociate competing motor programs from spatial interference, one has to present stimuli either vertically aligned or sequentially at a central location. Thus the response program activated by a stimulus would not depend on its spatial location. Examples of such tasks include the Stroop task (Mead, Mayer et al. 2002), where two features of the same stimulus, for example colour and text, have either congruent or incongruent response associations or a vertically aligned version of the Eriksen flanker task with distracting flankers positioned above or below the target (Mattler 2006).

Despite the fact that parietal areas are often activated in interference tasks such as the Stroop and Eriksen flanker paradigms in healthy individuals (Botvinick, Nystrom et al. 1999; Casey, Thomas et al. 2000; Bunge, Hazeltine et al. 2002), there have been very few studies looking at non-lateralised effects of parietal lesions on conflict processing and cognitive control (Posner, Walker et al. 1984; Chieffi, Gentilucci et al. 1993; Ro, Cohen et al. 1998; Husain, Mattingley et al. 2000; Lavie and Robertson 2001; Pujol, Vendrell et al. 2001; Snow and Mattingley 2006). Pujol and colleagues did investigate non-lateralised cognitive control function in patients with both parietal and frontal lesions using a Stroop task (Pujol, Vendrell et al. 2001). However, these patients suffered with multiple sclerosis and neglect was not documented within the group. The patients were classified as having predominant parietal or medial frontal disease or neither of those two regions predominating for comparison, but inference is extremely limited as white matter lesions of multiple sclerosis are scattered throughout the brain and spinal cord. Given these restrictions, it is interesting to note that the interference cost was *reduced* in patients with predominant parietal damage and *increased* in patients with medial frontal damage suggesting perhaps that competing responses are processed less when integrity of parietal lobe is impaired.

In summary, control over interference from distractors appears to be abnormal in patients with neglect. While the role of the PPC may not be purely motor or sensory, evidence presented above suggests that parietal damage does disrupt conversion of sensory signals into behaviour at some level of visuomotor

planning. In this thesis, the hypothesis that reaching deficits in neglect actually reflect failure of response competition between directional motor programs is explored, but first the basis of this hypothesis is discussed further.

1.3 Hypothesis

When multiple responses are possible, we have to choose the most appropriate action. Efficient action selection must be based on the current sensory environment, as well as ongoing goals and previous experience. Brain areas involved in action selection should therefore be sensitive to sensory stimuli as well as having task, or context sensitivity. PPC neurones code motor commands (Andersen and Buneo 2002) as well as sensory events (Bisley and Goldberg 2003) and respond differentially according to the number of possible responses associated with a stimulus (Stoet and Snyder 2007). In addition, there are task or context dependent cells in PPC (Stoet and Snyder 2007). Therefore, PPC has the appropriate functional characteristics for an area involved in response competition.

Directional biases exhibited by patients with neglect following right hemisphere stroke have been difficult to explain, with some authors suggesting a directional motor deficit and others proposing a sensory visuomotor deficit (Mattingley, Husain et al. 1998; Husain, Mattingley et al. 2000; Sapir, Kaplan et al. 2007). Here we suggest that *directional competition between action plans is resolved abnormally* in patients with right PPC stroke and neglect.

In normal PPC, when a decision between leftward and rightward movement is made, the two competing directional representations could be considered to inhibit each other resulting in a small delay in response (Cisek 2007). If competing leftward action plans are not propagated normally within the right parietal lobe, one would expect that patients with right PPC damage would manifest a rightward motor bias; rightward movements would be relatively disinhibited. This would result in directional hypokinesia being most marked when response choice is not predefined with 100% certainty, i.e., when there is potential response competition.

However this is not to say that PPC is the only area where response competition occurs. There is evidence that a network of areas may feed forward to influence motor output, including regions in lateral premotor and medial frontal cortex (Cisek and Kalaska 2002; Cisek and Kalaska 2005; Cisek 2007). While response competition (and consequent behavioural delay) may occur in PPC, other regions – perhaps in prefrontal cortex – may selectively inhibit or facilitate certain responses according to behavioural goals and context (Botvinick, Cohen et al. 2004; Scerif, Worden et al. 2006; Sumner, Nachev et al. 2007). Cisek has recently suggested just such interaction, with both PPC and prefrontal computations converging on dorsal premotor cortex (**Fig 1.8**- (Cisek and Kalaska 2002; Cisek and Kalaska 2005; Cisek 2007)).

Cisek recorded from the dorsal premotor cortex (PMd) of rhesus monkeys and found that when two stimulus-response associations were activated (**Fig 1.8a),** both were initially represented (Cisek and Kalaska 2005). Specifically, when

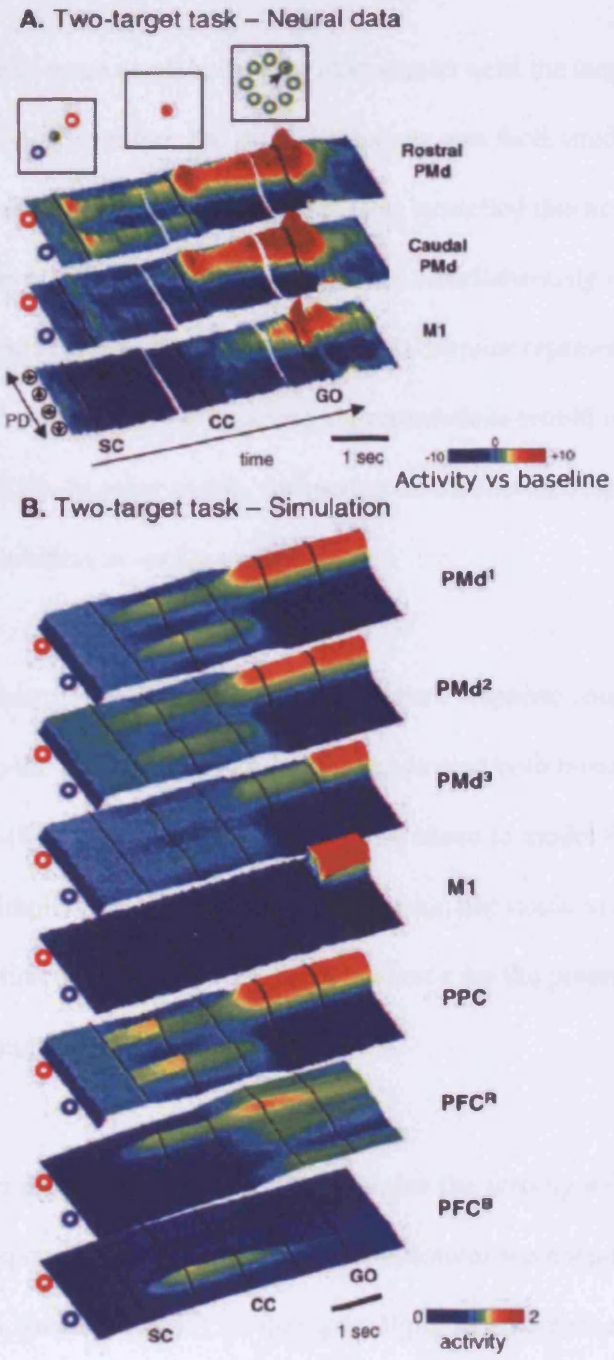


Figure 1.8 Neural activity during a decision task and activity predicted from computational model Cisek 2006

Two possible targets are presented: one red, one blue (A). Then, the colour of the central target indicates which one of the targets is correct and then the GO signal (green circles) indicates that the monkey should reach towards the correct target. Neuronal activity in rostral dorsal premotor cortex (PMd) shows that two potential actions are specified initially with one being facilitated and the other inhibited. In contrast, in M1, only the appropriate action is represented at the end of the decision process. Therefore, rostral PMd appears a likely site for integration of signal response processing within multiple streams including PPC and prefrontal cortex.

B is a simulation of this two target task. Both potential targets are represented in PMd and PPC.

two potential targets were cued, both were represented until the target for the reach was specified. Thereafter, the correct response was facilitated and the least appropriate representation inhibited. He later modelled this activity suggesting that several potential action plans were simultaneously represented within fronto-parietal processing streams (**Fig 1.9**). Similar representations would excite each other, whereas opposing representations would inhibit one another (Cisek 2007). In other words, competing or conflicting response plans lead to mutual inhibition in such a model.

Cisek proposed that the PPC would be one site where response competition would occur with the population of neurons representing both possible response choices (**Fig 1.8b and 1.9**). Although he chose to model PPC as it has been previously implicated in visuomotor processing, one could argue that the computer simulation does not provide direct evidence for the presence of neurons coding multiple response choices in PPC.

However, another recent paper did directly examine the activity within PPC neurons when response choices between two alternatives were made (Scherberger and Andersen 2007). In their paradigm, Scherberger and Anderson trained rhesus monkeys to reach towards one of two targets (Scherberger and Andersen 2007). The monkey was free to choose the targets, but the interval between presentation of the two targets was altered such that the monkey chose evenly between the two.

Activity within neurons of the PPC was correlated with response choice, i.e. the cells were not simply responding to the presence of the target, but the intention to act towards the target (Scherberger and Andersen 2007). Thus there is neurophysiological basis for the proposition that response choice competition occurs between cells in PPC.

In the next section we present evidence on how PPC and other brain areas are thought to be involved in response competition. Paradigms such as the Eriksen flanker and Stroop tasks have often been used to investigate response competition in humans (Botvinick, Nystrom et al. 1999; Casey, Thomas et al. 2000; Bunge, Hazeltine et al. 2002; Botvinick, Cohen et al. 2004). In these tasks there is always one correct response, and the interfering information engenders representations of incorrect responses that are thought to compete leading to delay (Eriksen 1995). Therefore, the flankers or incongruent interfering information can be thought of as analogous to the incorrect response option in the task used by Cisek (**Fig 1.8a** - Cisek and Kalaska 2005) and also to the response plan that is not chosen in the free choice paradigm used by Sherberger and Andersen (Scherberger and Andersen 2007). All of these paradigms require subjects to resolve competition between possible responses.

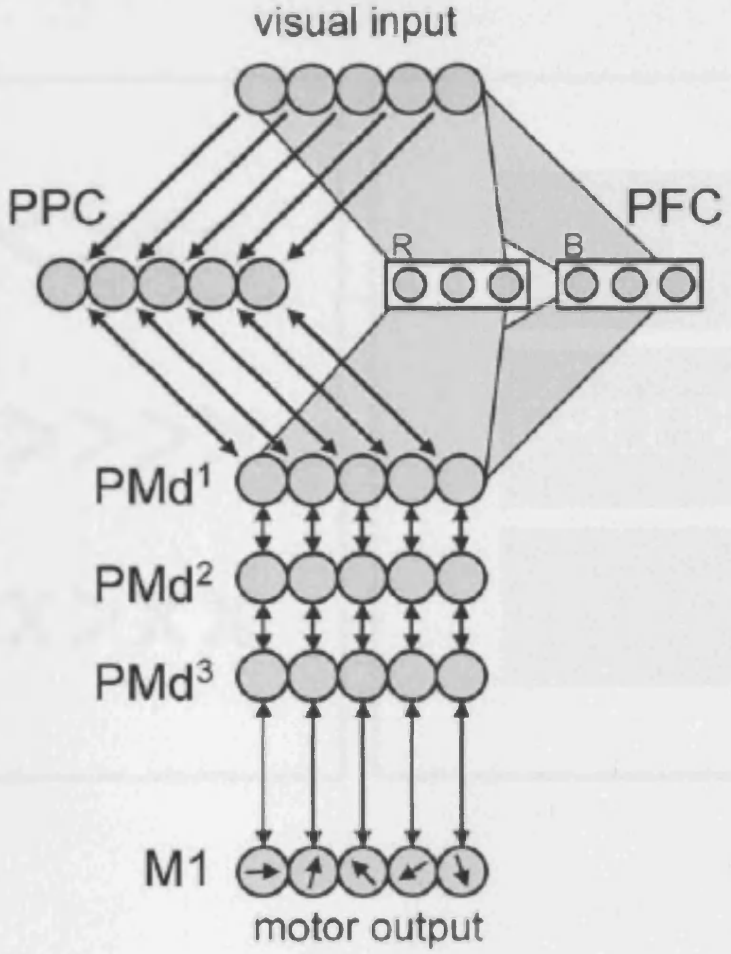


Figure 1.9 Computational model of action selection from Cisek 2006 and 2007
Each neural layer is depicted by a set of circles representing cells with different preferences for a movement parameter (e.g. direction). Thin arrows represent topographic connections (in most cases reciprocal) between layers involved in action specification. Grey polygons represent the input to and from prefrontal cortex, which is divided into two subpopulations each preferring a different stimulus colour. These projections are also topographic, but with much lower spatial resolution. Visual inputs are presented to the input layer, and the GO signal gates activity in primary motor corte
Abbreviations: PPC, posterior parietal
cortex; PFC, prefrontal cortex; PMd, dorsal premotor cortex; M1, primary motor cortex

We propose that competing action plans propagated within PPC mutually inhibit each other resulting in the delay in activity found when responses compete. Control over interference from competing responses is often thought to involve cognitive control systems that allow flexible adaptation of behaviour and the role of the PPC is discussed in the context of the cognitive control literature.

1.4 Cognitive control: flexible action selection

Cognitive control is a broad term used to describe flexible adaptation of behaviour to meet current demands (Botvinick, Cohen et al. 2004). One problem with investigating such control processes is that we have no *a priori* knowledge of the modules of control activity within the brain. When faced with a difficult task, one could imagine that increasing alertness, error monitoring, filtering of distracting information or inhibiting inappropriate motor plans could all result in improved performance. Some observers have suggested separate systems operate for all these and other facets of cognitive control, with interaction between different components essential particularly for say updating strategy when an error has been detected, or implementing rule changes that might alter which response is appropriate (van Veen and Carter 2002; van Veen and Carter 2005).

An alternative, but perhaps complementary, view is that there are high-order abstract executive control functions common to many cognitive operations (Norman and Shallice 1986; Duncan and Owen 2000). Carter and colleagues point out that monitoring and resolution of conflict could be a process shared

by many situations requiring cognitive control (Carter, Botvinick et al. 1999). For example, there is conflict when motor plans compete and a choice must be made (Botvinick, Nystrom et al. 1999; Liston, Matalon et al. 2006); during commission of an error there is conflict between the actual and the desired response (Carter, Braver et al. 1998); and when rapid strategy changes are required there is conflict between the familiar and new responses to a stimulus (Liston, Matalon et al. 2006). Dissociating cognitive control processes has been attempted using functional imaging studies although these show brain activity associated with rather than critical for a particular function. Lesion studies, on the other hand, could reveal selective damage in cognitive subsystems and whether brain regions are critical for such functions. But very few have been designed to investigate such control deficits (Turken and Swick 1999; Swick and Jovanovic 2002; Swick and Turken 2002; Aron, Fletcher et al. 2003; Ullsperger and Yves von Cramon 2006; Sumner, Nachev et al. 2007).

It should be noted that considering 'control' regions within the brain is not useful if one cannot explain how that region is activated by external stimuli and contextual information. Description of control processes should not rely on central command, ' executive', or a homunculus within our brains guiding behaviour (Sumner, Nachev et al. 2007).

Can we then really differentiate 'control' processes from any other activity occurring within the brain? One approach to this question is to distinguish between *automatic* or reflexive activity as opposed to flexibly implemented brain processes that may occur only under certain circumstances. An example

of an automatic action is perhaps rapid gaze shift and fixation of a salient visual event, sometimes considered to be a stimulus-driven or 'bottom up' response. A flexible process might be the choice to change pedals in the car when we see a traffic light change from red to green, a goal driven or 'top down', controlled action. But there are many similarities between these two processes; both are the result of neural activity generated by a sensory environment in the context of neuronal adaptation based on previous experience. In addition, neither action is inevitable as both can be overcome – even salient events can be ignored and if a person steps out in front of the car, the pedal change would be delayed.

Therefore, one might consider all behaviour as the result of stimulus-activated response plans. Many channels may operate in parallel to process stimulus response activations, but these would need to converge to form coherent motor output. As we have seen in **section 1.3**, there is evidence that multiple motor plans are activated when a response is planned and that information regarding the action to be undertaken accumulates within premotor cortex until a decision threshold is reached (Cisek 2007). It would not be expected that all processing streams process information in exactly the same way. Competition between action plans may be biased differentially across brain regions according to distinct characteristics of neurons within each area, for example, hypothetically, one brain region may have a centre-surround type inhibition where information at the fovea is processed preferentially, whereas another area may selectively propagate the most novel information.

Therefore, rather than one neuronal group 'controlling' another, several processing streams may combine and depending on the strength of each, motor output is determined. Consistent with the idea of multiple parallel motor processing streams, in monkeys the premotor cortex has connections to and from inferior and superior parietal regions, as well as medial prefrontal cortex (Ghosh and Gattera 1995; Rozzi, Calzavara et al. 2006). In humans, functional imaging has demonstrated that widespread networks of areas, including parietal and frontal regions, are activated when movements are planned (Elsinger, Harrington et al. 2006).

For these reasons, the term 'control' when applied to brain processes should perhaps be avoided and it is used here only to be in keeping with the large body of 'cognitive control' literature. In this thesis 'control' refers to processes that may modulate but not be critical for behaviour. The rationale for this distinction is pragmatic as it separates patients with hemiparesis or hemisensory loss from those with more subtle deficits in motor programming. While patients with left neglect may have a full range of movement even with their left arms, under certain circumstances they may fail to move (motor neglect) or lose some of their premorbid motor refinement (e.g. directional hypokinesia). This is in stark contrast to patients with hemiparesis who have damage in the primary motor pathways and are unable to move their limbs at all. In this case, a critical motor output pathway or combination of pathways may be damaged, although multiple other areas that feed-forward to influence motor output and modulate behaviour in certain situations may still be intact .

In the next section we discuss experimental paradigms used to investigate behavioural modulation or control. These include the Eriksen flanker and masked prime tasks which are used in the experimental chapters of this thesis and therefore discussed in detail as well as the Simon task (spatial conflict), Stroop task and task switching experiments which are referred to only where pertinent. Thereafter, the cognitive control systems uncovered using these paradigms are discussed, divided into sections on medial and lateral prefrontal and posterior parietal regions.

1.4.1 *Generating competition: interference paradigms*

Much of the work underlying our understanding of flexible control of behaviour when responses conflict stems from interference paradigms such as the Eriksen flanker task (Eriksen and Eriksen 1974; Botvinick, Nystrom et al. 1999; Bunge, Hazeltine et al. 2002; Durston, Davidson et al. 2003; Blasi, Goldberg et al. 2006, e.g. **Fig 1.10a**). In this task subjects respond according to a central cue and ignore peripheral flanking stimuli. Often the central cue is an arrow and the flankers may be congruent with the cue (pointing in the same direction), incongruent (pointing in the opposite direction) or neutral, i.e. they don't carry any directional information. Another paradigm widely used to investigate conflict is the Stroop task (MacDonald, Cohen et al. 2000; Pujol, Vendrell et al. 2001), where subjects are asked to report the colour of the print used to type a word and the text of the word can either name the same colour (congruent) or a different colour (incongruent - **Fig 1.10**). Consistently, it has been shown that normal subjects are slower to respond and make more errors in the incongruent than congruent condition of these two tasks.

Reaction time delay in the incongruent condition is thought of as the cost of interference due to processing of competing information (Eriksen 1995). In the Eriksen flanker task, when flanking letters are different from the target but have no response association, the delay is much less than when flanker letters are different and carry a conflicting response association (Eriksen 1995). Therefore, competition between motor responses rather than sensory representations is thought to account for most of the incongruent response delay.

Not only do these interference paradigms provide a window onto modulation of motor performance directly within a trial, but they also show how motor and cognitive control mechanisms influence behaviour according to the context on a longer term basis (Gratton, Coles et al. 1992). In the Eriksen flanker task, the size of the incongruence reaction time cost is affected by the preceding trial type (Casey, Thomas et al. 2000; Scerif, Worden et al. 2006); the delay is reduced when an incongruent stimulus follows another incongruent stimulus (Gratton, Coles et al. 1992). While a proportion of this reduction is due to repetition priming of stimuli (Mayr, Awh et al. 2003), some of the adaptation cannot be explained by simple stimulus recurrence and is thought to reflect modulation of activity in areas processing response competition (Ullsperger, Bylsma et al. 2005).

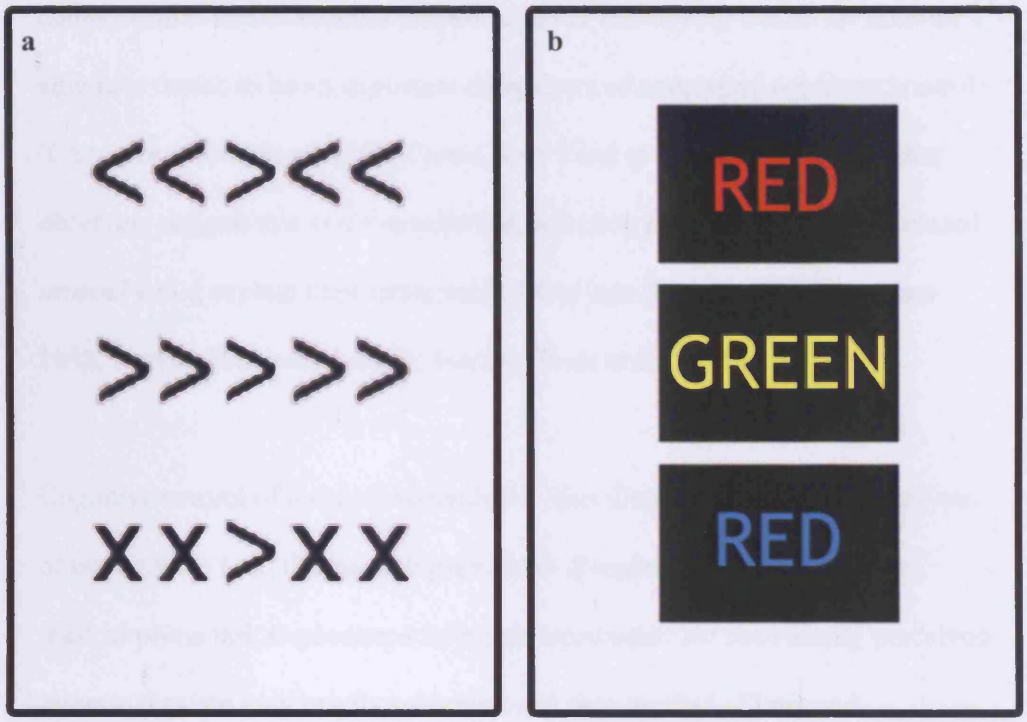


Fig 1.10 Eriksen flanker and Stroop tasks
In the Eriksen flanker task (a), subjects have to respond to the central target arrow and ignore the peripheral flankers. Consistently, a response delay has been shown when the flaking arrow are incongruent (top row), compared to when they are congruent (middle row) or neutral (bottom row). Likewise, reading the word in the Stroop task (b) is delayed when the colour is incongruent (bottom two boxes).

The nature of these contextual control processes has been a matter of intense debate. Carter and colleagues propose *conflict monitoring* within the anterior cingulate cortex to be an important component of contextual cognitive control (Carter, Botvinick et al. 1999; Carter, Van Veen et al. 2001), whereas other observers suggest that *error monitoring*, *selection for action* or even increased *arousal* could explain their experimental findings (Posner and DiGirolamo 1998; Braver, Barch et al. 2001; Nachev, Rees et al. 2005).

Cognitive control of motor competition is also illuminated using another type of interference task, the masked prime task. Response competition in the masked prime task is generated by prime arrows that are not visually perceived because they are very briefly presented and then masked (Eimer and Schlaghecken 1998). Despite not being visually perceived, the masked arrow still affects subsequent performance when a speeded response is required to a target arrow (**Fig 1.11a**).

Critically, the effect of the prime on the target is dependent upon the duration between onset of the mask and onset of the target (Eimer 1999; Eimer and Schlaghecken 2001; Eimer, Schubo et al. 2002). If the mask and target are separated by a short duration of <50ms, then incongruent primes tend to slow and congruent primes speed performance, similar to classical priming effects (**Fig 1.11b**). However, if the prime and target are separated by a longer interval of ~200ms, the reverse effect is seen. Prime arrows that point in the same direction as the target result in *slowed* reaction time to the target. This paradoxical slowing is called the negative compatibility effect (NCE – **Fig**

1.12c). So, for example, if a right prime is first presented and then masked and then after 200ms a right target arrow is presented, the response to the target is slower than if the prime were either a neutral square or a left prime (**Fig 1.12d**).

Much investigation has focussed on the reason for the negative compatibility effect. Why would compatible prime arrows cause slowing? ERP data have suggested that in fact the primes initially cause activation in the direction of the prime, but that this activation is subsequently inhibited leading to favouring of the alternative response (**Fig 1.11 and 1.12**). This *automatic inhibition* is thought to prevent us acting on the basis of the very short, irrelevant prime cue, i.e. it reflects inhibition of motor programs that are not subsequently carried out (Eimer and Schlaghecken 1998; Eimer 1999; Eimer, Schubo et al. 2002; Seiss and Praamstra 2004; Seiss and Praamstra 2006; Sumner, Nachev et al. 2007; Sumner 2008). Such an inhibitory mechanism would refine movement resulting in only appropriate responses occurring.

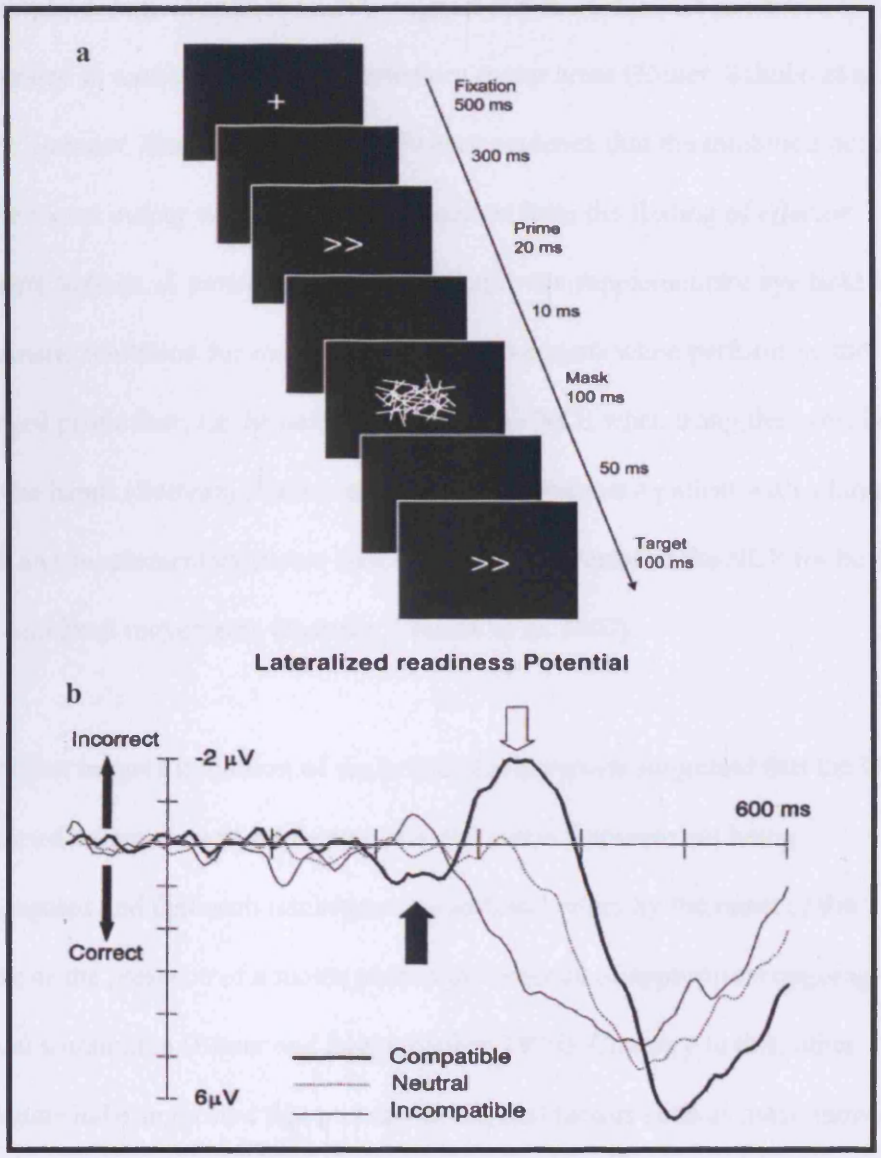


Fig 1.11 Masked prime paradigm and ERP responses
(a) shows a typical masked prime paradigm in which a negative compatibility effect (slowing when prime and target point in the same direction) is obtained. ERP responses following congruent, incongruent and neutral masked primes are shown (b). Note the change in polarity (marked by solid and unfilled arrows) for compatible (congruent) stimuli over time.

Neurophysiological and lesion data suggest that the automatic inhibition is generated in medial frontal supplementary motor areas (Eimer, Schubo et al. 2002; Sumner, Nachev et al. 2007). Further evidence that the inhibition occurs at the motor output stage of processing comes from the finding of *effector specific* deficits. A patient with a tiny lesion in the supplementary eye field lost automatic inhibition for eye, but not hand movements when performing the masked prime task, i.e. he had a reversal of the NCE when using the eyes, but not the hands (Sumner, Nachev et al. 2007). In contrast a patient with a larger SEF and supplementary motor area lesion had a reversal of the NCE for both eye and hand movements (Sumner, Nachev et al. 2007).

But what triggers inhibition of the prime? Early reports suggested that the NCE reflected automatic self-inhibition of motor plans that were not being propagated and that such inhibition was initiated either by the onset of the mask or the presence of a motor plan in the absence of appropriate ongoing visual stimulation (Eimer and Schlaghecken 1998). Contrary to this, other accounts have suggested that perhaps perceptual factors such as mask-induced priming or prime-induced alteration of the saliency of the target may contribute to the NCE (Klapp and Hinkley 2002; Lleras and Enns 2004; Sumner 2007).

Most masks used in experiments where a NCE has been found comprise either arrows in both directions (Eimer and Schlaghecken 1998) or randomly generated diagonal lines . In both cases, the features within the mask that are not in the prime may be processed in a privileged way simply because they are novel and this could result in priming in the opposite direction to the prime.

However, while a proportion of the NCE may result from this mask-induced priming, even when this is controlled for there is still significant negative priming, suggesting that this is not the whole explanation (Sumner 2008). In addition, when prime and target are at different locations, a NCE can still occur, making perceptual priming at a given location an unlikely cause of the NCE (Sumner, Tsai et al. 2006; Machado, Wyatt et al. 2007). Overall, it is considered that the majority of the NCE results from activation of a *motor plan* that is subsequently inhibited rather than perceptual interactions.

One interesting question regarding all these interference paradigms (masked priming, Eriksen flanker, Stroop) is whether or not they all involve the same cognitive operations. For example, all require selection between competing responses. Therefore one could consider that they were tapping into at least one similar cognitive process. However, it is equally possible, that brain systems involved in inhibition of flanker induced response plans differ from those that automatically inhibit masked primes. In order to explore these possibilities, one could ask whether lesions in certain areas interrupt processing in similar or distinct manners across these different interference tasks.

Much of the research into cognitive control has focused on activity within prefrontal areas. Therefore medial and dorsolateral prefrontal cortices are discussed separately prior to exploring the possible role of posterior parietal cortex in flexible control over behaviour.

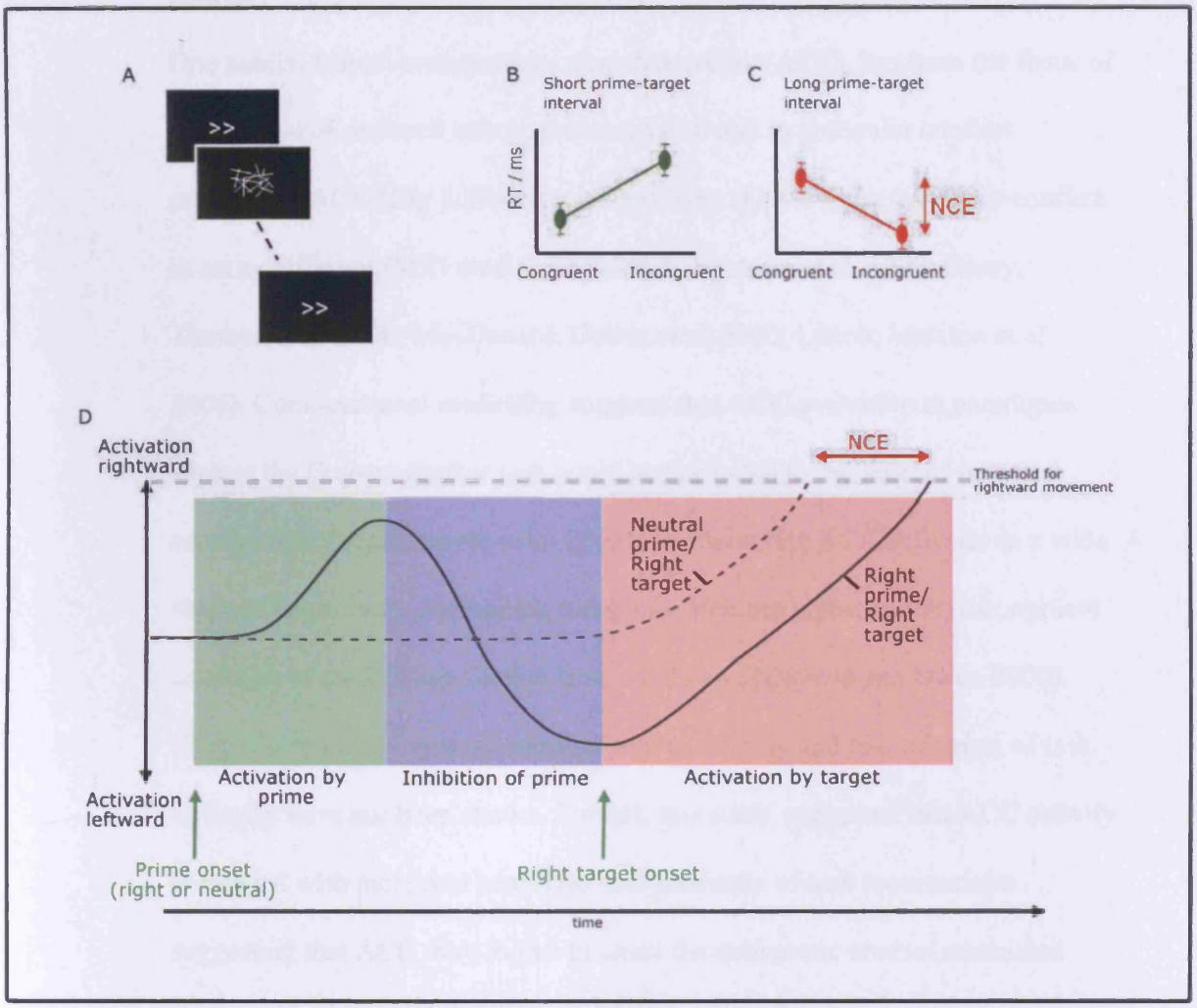


Fig 1.12 Masked prime paradigm and ERP responses
The effect of the masked prime is dependent on the duration between the prime and the target (A). When the interval is *short* (B), incongruent arrows cause a delay, but when the interval is *long* (~200ms), congruent arrows cause a delay (C). D shows a schematic of brain activity in response to the prime (activation in the direction of the prime), then subsequent inhibition (resulting in activation in the opposite direction) and then activity related to the target when the primes are either neutral (dashed line) or rightward (solid line). NCE = negative compatibility effect.

1.4.2 *Medial Prefrontal Cortex: conflict detection, response selection or arousal?*

One medial frontal area, anterior cingulate cortex (ACC), has been the focus of a great deal of research into cognitive control and in particular conflict processing. ACC (**Fig 1.2**) activation has been shown when responses conflict in many different fMRI studies (Botvinick, Nystrom et al. 1999; Casey, Thomas et al. 2000; MacDonald, Cohen et al. 2000; Liston, Matalon et al. 2006). Computational modelling suggests that ACC activation in paradigms such as the Eriksen flanker task could be attributed to the level of response conflict (Botvinick, Braver et al. 2001). However, the ACC activates in a wide range of cognitively demanding tasks, of which the high-conflict, incongruent condition of the Eriksen flanker task is only one (Duncan and Owen 2000). Clear dissociations between conflict-related activity and the influence of task difficulty have not been shown. Further, one study suggested that ACC activity correlated with increased heart rate independently of task requirements suggesting that ACC may in fact mediate the autonomic arousal associated with conflicting or difficult situations (Critchley, Mathias et al. 2003).

Nevertheless Carter and colleagues propose that the role of the ACC is to *monitor* the degree of *conflict* (Carter, Braver et al. 1998). After detecting conflict, rather than mediating resolution of conflict itself, they suggest that the ACC recruits other regions, notably the lateral prefrontal cortex (LPFC) and posterior parietal cortex (PPC) that then implement changes in cognitive control in response to the presence of conflict (Kerns, Cohen et al. 2004; Ridderinkhof, van den Wildenberg et al. 2004; Egner and Hirsch 2005).

There are several challenges to the idea of the ACC as a generic conflict monitor. The first is that both humans and monkeys with ACC lesions do not show deficits on all tasks requiring conflict resolution (Stuss, Bisschop et al. 2001; Swick and Jovanovic 2002; Rushworth, Hadland et al. 2003; Rushworth, Walton et al. 2004; Fellows and Farah 2005). Neither were consistent changes in event-related electrical activity following high conflict situations demonstrated in a subject with an ACC lesions (Swick and Turken 2002). Electroencephalographic study of one patient with a lesion of the ACC revealed that the event-related potential (ERP) component, N450, which follows incongruent stimuli was increased, whereas, the error related ERP signal, error related negativity, was attenuated (Swick and Turken 2002). Detailed ERP studies on normal individuals have led to suggestions that error-related and response conflict-related activity occur in different parts of the ACC (van Veen, Holroyd et al. 2004). However, if the ACC is acting as a generic conflict detection centre, it should be similarly activated by both commission of errors and response competition.

The next major challenge comes from fMRI studies that have not shown ACC activation during tasks that involve conflict (Milham, Banich et al. 2003; Nachev, Rees et al. 2005). In one of these studies subjects were either instructed or had a free choice to initiate an eye movement leftward or rightward (Nachev, Rees et al. 2005). On 50% of trials, a variable time after the onset of the cue to initiate a saccade, subjects were instructed to change direction. In this high conflict, change-of-plan condition, BOLD responses

were found in the rostral pre-supplementary areas (pre-SMA) and not in the ACC (**Fig. 1.2**). The index of volition, the free choice condition, revealed activity in the caudal pre-SMA consistent with one other study suggesting a role for the pre-SMA in internal generation of movement (Lau, Rogers et al. 2004). Thus, different areas within the pre-SMA are involved in selecting between conflicting motor plans and volitional control of movement. Further, the lack of ACC activation means that its proposed conflict monitoring role does not generalise to all situations.

Rather than being a conflict monitor, the role of the ACC may be in the translation of emotional or motivational states leading to increased arousal into the physiological autonomic responses (Paus 2001; Critchley, Mathias et al. 2003). The ACC has connections to motor cortical and spinal areas, dorsolateral prefrontal cortex (DLPFC) and limbic areas including the thalamus which make it well connected for mediating physiological responses to high arousal states (Paus 2001). High conflict situations may in fact be activating the ACC because of the increased arousal associated with these stimuli.

Establishing the function of the ACC and other regions within the medial frontal cortex is made more difficult by the fact the medial frontal lesions following stroke or tumour resection tend to be large limiting the inference that can be made about small sub-regions. The proximity of areas such as the pre-SMA and ACC is extremely close, so individual variation can mean resolution of these structures challenges most MRI scanners (**Fig 1.2**). However, a recent study investigated motor control using the masked prime paradigm in two

patients with very small lesions, one involving the supplementary eye field (SEF) and the other both SEF and SMA, identified using seven tesla magnetic resonance imaging (Sumner, Nachev et al. 2007). In both patients, there was a reversal of the NCE found in normal subjects. In the patient with just SEF damage, this reversal occurred only when he responded using his eyes. In contrast, the patient with SEF and SMA damage had the abnormality for both eye and hand movements.

These tiny lesions were associated with reversal of the normal inhibitory processes that control movement, but it is important to note that the prime arrow still had an effect on performance. Motor priming still occurred, even though normal inhibition was lost. If the SMA and SEF were the only areas normally involved in processing competing responses, one would not expect the prime to have any effect on the target. However, there was evidence in these patients with medial frontal damage of priming, presumably occurring in other intact brain regions. Therefore, these lesions unmasked a second process. Thus there appear to be at least two and possibly more parallel processing streams for signal response associations.

In summary, there appears to be functional fractionation within the medial prefrontal cortex (Picard and Strick 2001). How such specialisation is organised is still unknown and can only be accurately assessed using techniques that allow high structural and functional resolution of brain areas and paradigms that explore the appropriate cognitive process and response modality. Although there is evidence that the ACC cannot be acting as a

conflict detector in all situations, it is still possible that processing conflicting stimuli is an intrinsically important process occurring within the cognitive control system.

1.4.3 *Lateral prefrontal cortex mediates flexible behaviour when circumstances change*

A meta-analysis of frontal activation during cognitively demanding tasks revealed that regions of lateral prefrontal cortex, like the ACC, are active during a diverse range of activities suggesting that these areas may subserve operations of fundamental importance for cognitive function (Duncan and Owen 2000). Although lateral prefrontal cortex (LPFC), like medial prefrontal, is stimulated by conflicting information (Botvinick, Nystrom et al. 1999), the pattern of activations suggests that rather than responding purely to the presence of conflict, LPFC is involved in maintenance and alteration of task rules (Miller and Cohen 2001; Sakai, Rowe et al. 2002). Since lateral and medial prefrontal areas seem to subserve different aspects of similar cognitive control processes, much emphasis has been placed on the interaction between the two areas.

The conflict monitoring hypothesis suggests that the ACC recruits DLPFC after detection of conflict (Ridderinkhof, van den Wildenberg et al. 2004). Trial-by-trial BOLD changes in ACC and DLPFC have shown that ACC activation on an incongruent trial not only predicts improved performance on a subsequent incongruent trial, but also increased DLPFC activity on that subsequent trial (Kerns, Cohen et al. 2004; Liston, Matalon et al. 2006).

Although these results are cited as evidence for recruitment of DLPFC by the ACC, in fact both regions could be independently responding to the context of the task. Further, there is evidence against the need for ACC to recruit DLPFC as, after a conflict task has been practised and become familiar, DLPFC activates autonomously without the need for prior ACC involvement (Milham, Banich et al. 2003).

Parris et al suggested that the LPFC is actually activated by attentionally salient perceptual events perhaps evaluating whether such events require a change in the behavioural rules (Parris, Thai et al. 2007). However, it seems likely that the LPFC is recruited in a task-specific way. For example, using a Stroop task, Macdonald and colleagues showed that the left DLPFC activates when subjects are given the instruction to name the colour of the text rather than read the word that names a colour despite the fact that these two instructions had similar perceptual salience (MacDonald, Cohen et al. 2000). Individuals with most left DLPFC activation when given the instruction had least Stroop interference when the trial began, suggesting more efficient performance on a task is related to DLPFC activation. This task-specific activation is consistent with the view of the lateral prefrontal region as an area in which current goals are represented in working memory (Miller and Cohen 2001).

While some parts of the LPFC, particularly perhaps the left DLPFC, appear to mediate changes in task rules, the right lateral prefrontal cortex may specifically have a role in inhibition of prepotent responses (Garavan, Ross et al. 1999; Aron, Fletcher et al. 2003; Aron, Robbins et al. 2004). Aron and

colleagues tested patients with right frontal lobe damage on a stop-signal response paradigm (Aron, Fletcher et al. 2003). In this task, 75% of the time subjects responded left or right according to an arrow. In 25 % of trials, this arrow was followed a variable time later by a beep which instructed them to withhold a response. The extent of damage in each of their subjects was plotted in five different frontal regions of interest that had been defined by previous functional imaging studies. Correlations between damage in each region of interest with each person's performance on this task revealed that patients with right inferior frontal damage were least well able to inhibit their original response. In support of this, fMRI work has suggested that there appears to be a right lateralised network for response inhibition including the lateral prefrontal cortex, insular, frontal limbic and inferior parietal lobe (Garavan, Ross et al. 1999).

In summary, fMRI studies have shown that LPFC regions are activated by conflict particularly in task-switching paradigms when the rules of an experiment are changed and subjects have to adjust their response to familiar stimuli and also when subjects are required to inhibit a prepotent response to a stimulus (Garavan, Ross et al. 1999; Konishi, Nakajima et al. 1999; MacDonald, Cohen et al. 2000; Swainson, Cunnington et al. 2003; Parris, Thai et al. 2007). Both these operations may underlie implementation of flexible behaviour.

1.4.4 *Posterior parietal cortex: stimulus-response decoding and response inhibition*

Parietal, along with medial and lateral frontal, activations have been found widely in functional imaging studies when responses conflict (Botvinick, Nystrom et al. 1999; Casey, Thomas et al. 2000; Cavina-Pratesi, Valyear et al. 2006), but little is known about the precise role of the parietal lobe (Liston, Matalon et al. 2006). The focus of this thesis is how patients with left neglect, who often have parietal damage, resolve competition between conflicting response plans. In particular, lesion data suggest that the right PPC is important for generating directional leftward response programs (**section 1.2.2**). Very little work has focussed on how competing directional response plans are processed within the parietal lobe, but some studies have investigated the role of parietal cortex in competition between other types of responses, for example button presses with one or both hands.

When an action must be selected from two or more possible options, the parietal lobe activates in neuroimaging studies (Jahanshahi, Jenkins et al. 1995; Botvinick, Nystrom et al. 1999; Casey, Thomas et al. 2000; Bunge, Hazeltine et al. 2002; Cavina-Pratesi, Valyear et al. 2006; Elsinger, Harrington et al. 2006; Lau, Rogers et al. 2006; Liston, Matalon et al. 2006; Mueller, Brass et al. 2007). In order to investigate the role of the parietal lobe in response competition, one study focussed on the parietal contribution to modulation of conflict processing according to context (Casey, Thomas et al. 2000). Using a variant of the Eriksen flanker task, Casey and colleagues compared brain activation when incongruent stimuli were preceded by either four incongruent

stimuli or four congruent stimuli (Casey, Thomas et al. 2000). As has been shown before behaviourally (Gratton, Coles et al. 1992), reaction time costs reduced when incongruent stimuli followed other incongruent rather than congruent stimuli. Adaptation to the increased proportion of incongruent stimuli suggests strategic adjustment of cognitive control to limit flanker interference.

Casey et al. reported that activity in the superior parietal lobe (superior frontal gyrus and cerebellum too) increased when an incongruent stimulus followed four incongruent stimuli whereas inferior parietal (and superior temporal) activity reduced. They explained these findings in terms of allocation of spatial attention. Superior parietal regions have previously been suggested to direct top-down distribution of spatial attention (Corbetta and Shulman 2002). Casey and her colleagues proposed that the superior parietal lobe mediated strategic focus of attention onto the central target after several incongruent trials. In contrast, they suggested the inferior parietal lobe normally broadens attention to include the peripheral visual field and deactivates after repeated incongruent stimuli to allow focus of attention on the central target.

Mattler has challenged this interpretation of their data by studying the effect of varying the proportion of incongruent trials on the interference costs of flankers close to and far away from the central target stimulus (Mattler 2006). More distant flankers cause less interference cost than flankers close to the central cue – the distance effect. Therefore, if a narrowed focus of attention is responsible for the performance improvement in blocks with a high proportion

of incongruent trials, subjects should have an increased distance effect in these blocks, i.e. they would have even less interference from distant peripheral flankers if the attentional focus was reduced. However, despite using 5 different paradigms, Mattler found that this distance effect was if anything reduced in blocks with a high proportion of incongruent trials, inconsistent with the attention allocation account of Casey and colleagues.

Further investigation into the role of the parietal lobe in response competition has suggested perhaps that the parietal lobe represents the selection of possible motor plans of which only one is implemented. Bunge and colleagues trained subjects to push a left or right-sided button in response to 4 different letters (Bunge, Hazeltine et al. 2002). Using an Eriksen flanker task where one of the letters was the central cue and the flankers were either congruent or incongruent letters or neutral asterisks, they showed that regions within lateral prefrontal cortex activated only in the *incongruent* compared with neutral or congruent conditions. Thus these prefrontal regions appeared to be involved in choosing between two competing responses.

In contrast regions within the left inferior and superior parietal lobe were activated not only in the incongruent, but also in the congruent compared to the neutral condition. In the congruent condition, there were two different letters representing the same direction, whereas in the neutral condition only one letter carried any associated direction. Therefore the increased parietal activation perhaps represented the increased number of stimuli that required interpretation or signal-response (S-R) relationships that needed decoding. However, these

data may be confounded as the neutral condition had fewer letters than the other two conditions, so there is a possibility that the left parietal lobe activity simply reflects counting the number of letters.

More recent work using fMRI and stimuli that were either houses or faces has supported this interpretation of the left parietal lobe as the site where S-R relationships are decoded (Cavina-Pratesi, Valyear et al. 2006). Subjects had to press a button every time they saw a stimulus (simple reaction time task), withhold a response when they saw one of the two stimulus types (go-nogo tasks) or choose one of two buttons they had been taught to associate with each stimulus (choice reaction time task). These authors showed that the left parietal lobe was activated more in a choice reaction time task and a go-nogo task where there were two stimulus response associations, than the simple reaction time task where there were two stimuli, but only one possible response. This second report suggested that it was more superior regions within the left parietal lobe that decoded S-R relationships and perhaps represented possible response options.

While these two studies illuminate the function of the left parietal lobe, many studies have found either bilateral (Liston, Matalon et al. 2006) or right-lateralised activation in the parietal lobe during tasks that require cognitive control (Botvinick, Nystrom et al. 1999; Garavan, Ross et al. 1999). Botvinick and colleagues showed that right parietal lobe is activated in the incongruent condition of the Eriksen flanker task whereas bilateral inferior parietal cortices modulate their processing of incongruent stimuli according to context

(Botvinick, Nystrom et al. 1999). In the incongruent situation in the Eriksen flanker task, subjects must both filter the sensory information and inhibit an unwanted response. The latter process, response inhibition, may be particularly relevant to the hypothesis being tested in this thesis as, if opposing directional plans are assumed to mutually inhibit one another, loss of competing leftward response plans would result in *disinhibition of rightward response plans*. Therefore loss of a competing response can also be considered as a failure of inhibition.

Inhibitory control of behaviour was investigated by Garavan and colleagues (Garavan, Ross et al. 1999) by presenting letters every 500ms and asking subjects to press one button when they saw an X and another when a Y was presented, but withhold a response when X and Y did not alternate. They found a widespread, right lateralised network of regions – including the angular gyrus of the inferior parietal lobe as well as frontal areas – activated when subjects were required to withhold a response. Thus the right parietal lobe appears to have a role in inhibition of an inappropriate response perhaps mediating selection of the most appropriate movement plan.

While some studies have suggested a motor role in response inhibition for the right PPC, Liston and colleagues propose that the parietal lobe responds to sensory rather than motor conflict (Liston, Matalon et al. 2006). They presented subjects with coloured discs overlaid with a grating. Discs were either red or green and each colour was assigned a button press. In addition, the grating was moving upward or downward and each direction was assigned one

of the same two buttons given to the colours. Three salience levels for colour and grating were created by changing the luminance of the colour and contrast of the grating. Their index of response conflict was trials when the colour and grating instructed different buttons and subjects had to ignore one of the two. Sensory conflict was assumed to occur when colour and grating instructed the same response, but the salience of the irrelevant dimension was high. The strongest effects were found on "switch" trials when there was a change in instruction regarding the dimension to be monitored (colour or grating).

When reporting their data they highlight an anatomical dissociation with medial frontal regions activating to *response conflict* and superior parietal regions being sensitive to *stimulus conflict.* However one problem with this interpretation is the fact that the sensory conflict was generated by a parameter that had an associated response and therefore it was not purely sensory. Also, although they do not emphasise it, they clearly show that the inferior parietal lobe was also activated in their pure response conflict condition.

In summary, functional imaging data for the role of the parietal lobe within the cognitive control system has been controversial. Some authors consider that the parietal lobe controls allocation of spatial attention in response to conflict (Casey, Thomas et al. 2000; Botvinick, Cohen et al. 2004). However, more recent data suggests that the parietal lobe may be involved in response selection perhaps by representing all possible responses (Bunge, Hazeltine et al. 2002; Cavina-Pratesi, Valyear et al. 2006). There appear to be differences between the roles of the left and right parietal lobe in some paradigms with the

left parietal lobe perhaps decoding complex signal response relationships while the right parietal lobe has a role in inhibition of potential response plans.

So far we have reviewed evidence for motor deficits in patients with neglect and found particularly that neglect patients are slow to initiate contralesional movement, directional hypokinesia. In addition, parietal cortex activates in functional imaging studies during situations of response conflict, when motor programs compete. The hypothesis to be tested in this thesis is that competing leftward responses are propagated within right PPC and that damage to the right PPC leads to a reduction in response competition from leftward motor programs resulting in relative disinhibition to the right.

1.5 Outline of thesis chapters

The remainder of this thesis investigates the possibility that motor deficits and cognitive control impairments occur in patients with visual and motor neglect perhaps contributing to the lateralised bias. Behavioural performance is directly related to lesion location using lesion-symptom mapping techniques.

Chapter 2 provides details of experimental design, technical information on behavioural and lesion mapping methods, and patient recruitment. In chapter 3, a variant of the Eriksen flanker task is run on right parietal and frontal patients with and without neglect, as well as on individuals with left parietal lesions and healthy controls. This task examines *directional* responses and the effect of irrelevant flankers on response competition. The findings reported in this

chapter suggest that the right PPC may have a crucial role in representing competing leftward response plans.

This is further investigated in chapters 4 and 5. Chapter 4 describes right hemisphere stroke patients' performance on a masked prime task where directional primes are invisible but nevertheless have an effect on subsequent congruent or incongruent action plans. By contrast, chapter 5 uses a free choice paradigm, where directional responses also compete but are not visually represented since participants freely choose to move in one direction or another.

To investigate whether there might be asymmetries of conflict processing in the normal brain, healthy subjects are tested using a variant of the Eriksen flanker task in chapter 6. Chapter 7 focuses on motor neglect (lack of use of the contralesional arm) and provides new insight into behavioural deficits and neuroanatomy of this disorder. Finally, the findings of all sections of the thesis are summarised and discussed in chapter 8.

Chapter 2: General methods

2.1 Subject recruitment

All subjects gave informed consent and the consent form had been approved by the relevant hospital ethics committee.

2.1.1 *Patients*

Patients were recruited from the National Hospital for Neurology and Neurosurgery, Charing Cross, St Thomas' and St Mary's hospitals. These patients were either recruited from the wards by me from 2004-2007 or had already been screened by other members of the laboratory and were identified from the neglect database held by the cognitive neurology group at the Institute of Cognitive Neuroscience. Hence there was some variability in the time since event and this is clearly documented for all patients.

The vast majority of patients had suffered a stroke, either infarction or haemorrhage. Very occasionally patients with tumours were also tested and this is clearly documented in the text. Right-handed patients of any age were included in the study. Exclusion criteria were: inability to comply with behavioural testing; bilateral lesions on imaging performed at the time of the clinical event; bilateral clinical syndrome and limited comprehension such that task instructions were not understood.

2.1.2 *Control subjects*

Right-handed age-matched control subjects were recruited from the Agewell centre in Hammersmith which provides fitness, dancing and writing courses for

over 50s. Subjects all performed normally on Bell's cancellation and line bisection tasks (see next section) and were excluded if they had any history of intracranial pathology or were on medication that could interfere with cognitive processing. Each group of age-matched controls was chosen from a pool in order that the group average age was close to that of the patients being tested.

2.2 Behavioural assessments

2.2.1 *Visual neglect*

Patients were identified as suffering from visual neglect if they showed a behavioural asymmetry on the Bells cancellation or line bisection tasks (**Chapter 1,** (Ferber and Karnath 2001)) such that they crossed at least 3 more Bells on the right than the left side of the cancellation task or had a 5mm or greater average rightward deviation on the line bisection task (average of three 17cm lines). These two tests are thought to identify slightly different groups of neglect patients, with the Bells cancellation as perhaps the more sensitive test of lateralised bias (Ferber and Karnath 2001) and the line bisection being particularly abnormal in those with more posterior lesions (Rorden, Fruhmann Berger et al. 2006). However, this distinction is far from clear-cut and therefore both tests were used to identify as may patients as possible which then allowed within-group comparison of behavioural performance, neglect severity and lesion location.

Non-neglect control groups were defined either as those who had never had neglect or those who showed no neglect at the time of the experimental testing

depending on the critical comparison sought. This will be clarified in each experimental protocol.

The age-matched control subjects were also tested for neglect using the Bells cancellation and line bisection. Normal performance was considered to be no evidence of lateralised bias on the cancellation task and in addition, normal subjects were expected to cancel at least 90% of Bells across both sides. Less than 5mm deviation from the centre of the 3 lines was considered normal performance on the line bisection task.

2.2.2 *Motor neglect*

Motor neglect can be difficult to differentiate from hemiparesis (Punt and Riddoch 2006). Therefore for experimental testing, we excluded patients who had weakness on neurological examination at the time of testing. All patients with motor neglect reported symptoms of failure to use the left arm or leg. In addition all patients had breakdown of movement when rapid alternating hand movement were required. A novel test for motor neglect was also carried out on all patients. This is described in detail in the **Chapter 7.**

Motor neglect patients were also screened for visual neglect and personal neglect (Cocchini, Beschin et al. 2001).

2.2.3 *Dyspraxia*

Ideomotor dyspraxia was assessed clinically by asking patients to copy three hand gestures and also mime tooth and hair brushing (Goldenberg 1999) .

2.3 Stimulus presentation

All experiments were programmed using Presentation software (Albany, USA) software and presented on a Sony Vaio laptop with a 15" screen (PCG-5A1M). Subjects were instructed to fixate centrally for all experiments and eye movements were monitored by the experimenter. Importantly all experiments were programmed so that new trials did not start until after the subject had responded in the previous trial. This was to limit the impact of impaired sustained attention that could cause right hemisphere stroke patients to miss events (Rueckart and Grafman 1996; Robertson, Manly et al. 1997).

2.4 Response devices

In some experiments, a joystick was used to make left or right directional responses. The desktop joystick was custom built by Traxsys (Ringwood, United Kingdom) and with a 6cm pole. It was fitted with a spring which automatically centred the pole. The dead-space was 1% of total movement and the joystick was polled every 10ms during movement. The critical reading was the time to move out of the deadspace either leftward or rightward (movement initiation time). The output file from Presentation software recorded the trial-type, movement initiation time and the direction of movement. Importantly, the polling of the joystick began after stimulus presentation, therefore data were not recorded during the stimulus presentation and the duration of the stimulus was added to the movement initiation time for all subjects. This did not affect the validity of the data as the longest stimulus presentation time was 200ms, any movement within this time would conventionally have been considered anticipation and excluded anyway.

In other experiments, where manual button presses were required, a Cedrus button USB box (San Pedro, USA) was used.

2.5 Experimental Design

Each experiment was divided into blocks and block length was established according to the different experimental questions with the constraint that it should not last more than 3 minutes to ensure that patients could easily comply without losing concentration. Instructions were given both verbally and in writing on the screen. A practice of 1 block was given to all subjects. Data from this block were not recorded. Unless otherwise stated, trial types were pseudorandomised with the constraint that each trial type should be presented the same number of times per block.

2.6 Behavioural data – statistics

All statistical tests were performed SPSS 11.0 (Chicago, Illinois), unless otherwise stated. Individual statistics are described in each chapter. The Kolmogorov-Smirnov normality test with Lilliefors correction was performed on each dataset to establish suitability for parametric tests ($p>0.05$). When data are presented graphically, error bars represent standard error of the mean unless otherwise stated.

2.7 Lesion mapping – MRICro

All patient lesions were acquired using MRICro software available at www.mricro.com and a touch sensitive tablet (Wacom, Saitama, Japan). The

source image was generally routine clinical imaging, either CT or MR, unless a high resolution MR performed for research purposes was available. The default yaw, pitch and roll were used and lesions were plotted on the CH2 template to create an ROI (region of interest) on the axial images at Z coordinates: 56, 61, 66, 69, 75, 85, 88, 92, 96, 102, 108, 120 (**Fig 2.1**). Since the pitch of the source images varied and differed from that of the template in some cases, subcortical and cortical landmarks were used to maximise the accuracy of copying the images. Individual lesions for each chapter are all displayed in **Appendix 2**.

The images were then either overlaid or subtracted in MRICro to show regions of brain damaged in a group of patients or the region specifically associated with a particular behaviour. Voxel based tests of statistical significance were performed using MRICron software.

2.8 Lesion mapping - MRICron

Lesion studies are useful because, unlike neuroimaging techniques such as functional MRI, they reveal regions of the brain *critical* for certain processes. However, there are many factors that may influence the degree to which one can confidently infer that damage in one area leads to a particular behavioural abnormality.

Most strokes are large and encompass several brain areas that subserve many modular functions. Strokes leading to neglect often result from infarction in the middle cerebral artery territory and these patients will have a stereotyped pattern of damage with certain voxels being more commonly affected than

Figure 2.1 Axial planes used for lesion mapping

others. Therefore, if one takes a group of patients who all behave in a certain way and looks for the commonest area to be damaged in these individuals, it will not be possible to differentiate those areas most susceptible to damage from those critically associated with behavioural abnormality.

In order to identify critical areas for a given process, a control group of patients can be used who do not show a behavioural deficit but have stroke in a similar territory. They would therefore be expected to share lesion overlap in areas susceptible to damage, but not those critical for a given function (Karnath and Perenin 2005).

A second problem with lesion–symptom mapping is that behavioural data from affected and control groups are often not parametrically distributed, for example, the control group could be performing optimally, whereas, the affected group have impaired performance leading to a skewed distribution. Further, in order to divide subjects into affected and unaffected groups, one has to decide on a cut-off point, for example, neglect and non-neglect patients may be separated on the basis of their performance on standard clinical tests. However, many of the patients who take part in research have performed these tests many times, are highly motivated to optimise their performance and have learnt strategies for completing tasks following previous feedback during physiotherapy and neuropsychology rehabilitation. Therefore, these tests may be insensitive to lateralised bias in some cases.

The Brunner Munzel rank order test overcomes many of these problems (http://www.sph.sc.edu/comd/rorden/mricron) (Rorden, Karnath et al. 2007). In this non-parametric test, continuous behavioural data are ranked at each voxel and regions associated with relatively low score (impairment) on a given test are identified. Thus no division of patients according to behavioural performance or lesion location is required. In addition no assumptions are made about the underlying distribution of the data. The Brunner Munzel statistic is described by:

$$t_{BM} = \frac{n_1 n_2 (\bar{r}_2 - \bar{r}_1)}{(n_1 + n_2)\sqrt{n_1 s_1^2 + n_2 s_2^2}}$$

where n_1 and n_2 denote the number of observations in each group and r_i refers to the group's mean rank within the pooled sample. This test is applied at *each* voxel under consideration and the two groups are those who have a lesion at this point compared with those who do not. The output of MRICro is a z-score at each location that is equivalent to the t statistic calculated above.

This Brunner Munzel test is more robust than a t-test when the assumptions of normality are violated (Rorden, Bonilha et al. 2007). Correction for multiple comparisons can be achieved using conventional Bonferroni correction, the false discovery rate or permutation testing (Rorden, Bonilha et al. 2007; Rorden, Karnath et al. 2007). In this thesis, Bonferroni correction is used as it is likely to be the most conservative of the three methods and post correction significance level of 0.05 is applied. Only voxels where 3 or more subjects

have lesions are included in the analysis. In addition, single significant voxels are disregarded and clusters of significant voxels are sought. This is because a single voxel may be significantly associated with behavioural abnormality by chance as the output of the Brunner Munzel test in MRICron is a z score with a normal distribution. Thus after correction for multiple comparisons, even if no areas are significantly associated with a behavioural effect, a small number of voxels may fall within the tails of the distribution and appear significant. However, these voxels would not be expected to cluster.

It is important to note that there are still some major limitations with this method of lesion mapping. Firstly, the lesions are drawn by hand from clinical CT or MR scans onto templates in MRICro, thus introducing observer error. In addition different clinical scans, even within the same hospital, produce images sliced at slightly different pitches. In this thesis, the compromise of using the default MRIcro pitch was chosen after some experimentation. Further, there are major differences in the sulcal landmarks between individuals and even heterogeneity in anatomical location of different functional units within the brain (Mesulam 1985). For these reasons, although precise coordinates at the centre of significant regions are given, lesion localisation is discussed in broad terms that cover many voxels, for example, posterior parietal vs inferior frontal cortex.

Finally, the influence of lesion volume on lesion symptom mapping can be difficult to interpret. In theory, lesion volume can be looked for as an independent variable predicting an effect or used as a covariate with

behavioural abnormalities. However, recent data suggest that lesion volume is not truly independent as it is related to lesion location (Husain and Nachev 2007); smaller lesions tend to affect subcortical central areas whereas larger lesions stretch out into the periphery. Therefore, behavioural abnormality associated with either larger or smaller lesions could actually be due to damage in a particular cortical or subcortical area respectively. With this caveat, lesion volume is calculated using MIPAV software (version 4.0.1, NIH, Bethesda, Maryland) and correlations are sought between lesion volume and behavioural performance where appropriate.

Chapter 3: Control over conflict during movement preparation: Role of posterior parietal cortex

3.1 Introduction

Successful behaviour requires animals to select appropriate actions in highly variable situations. If the response is invariantly defined by the stimulus or environmental context, there is no difficulty for selection. Frequently, however, there is more than one possible action choice. Under these circumstances, there is potential conflict between response plans and it is necessary for brain mechanisms to select the best response to achieve the animal's goal.

Although most studies have focused on the role of prefrontal regions (Gehring and Fencsik 2001; Ullsperger and von Cramon 2001; van Veen, Cohen et al. 2001; Garavan, Ross et al. 2003; Botvinick, Cohen et al. 2004; Ridderinkhof, Ullsperger et al. 2004; Rushworth, Walton et al. 2004; Egner and Hirsch 2005; Nachev, Rees et al. 2005), it is clear that conflicting potential responses evoked by the stimulus environment are also associated with parietal activity (Bunge, Hazeltine et al. 2002; Liston, Matalon et al. 2006; Stoet and Snyder 2007). However, the role of posterior parietal cortex (PPC) in situations of conflict has not been extensively studied. Indeed, because previous studies have examined only activity in intact PPC, and not what occurs following lesions to this region, it remains to be established if the PPC is necessary for behaviour under these circumstances.

The hypothesis being tested in this thesis is that the PPC plays an important role in the *selection of action* under situations of response conflict, when

stimulus-evoked responses activate conflicting action plans. In humans, damage to the PPC, most prominently in the right hemisphere, often leads to the syndrome of unilateral neglect in which patients tend to be unaware of objects to their left (Humphreys and Jane Riddoch 2001; Doricchi and Tomaiuolo 2003; Mort, Malhotra et al. 2003; Robertson 2003; Hillis, Newhart et al. 2005; Bartolomeo, Thiebaut de Schotten et al. 2007). In addition to perceptual and attentional factors that contribute to neglect of leftward items (Duncan, Humphreys et al. 1997; Driver and Mattingley 1998; Mesulam 1999; Husain and Rorden 2003), some investigators have also reported directional motor deficits resulting in delayed reaching to contralesional objects – *directional hypokinesia* (DH) – in patients with neglect following either parietal or frontal lesions (Ladavas, Umilta et al. 1993; Behrmann and Meegan 1998; Mattingley, Husain et al. 1998; Coulthard, Parton et al. 2006; Sapir, Kaplan et al. 2007). However, the role of the PPC in motor control has been highly contentious and no clear consensus has emerged from studies in either humans or monkeys. Thus while some authors have presented data in support of a key role in programming spatially directed action (Milner and Goodale 1995; Snyder, Batista et al. 1997; Wascher, Reinhard et al. 1999; Battaglia-Mayer, Caminiti et al. 2003; Rushworth, Johansen-Berg et al. 2003; Gail and Andersen 2006), others have argued that these findings may be explained by the visual or attentional functions of the PPC (Colby and Goldberg 1999; Wardak, Olivier et al. 2004; Goldberg, Bisley et al. 2006; Gottlieb 2007).

To investigate the hypothesis that one important role of the PPC might be selection of action when stimulus-evoked responses activate conflicting action

plans, the effect of response conflict on directional movement in PPC patients with neglect was explored. Many studies of conflict in healthy individuals use variations of the Eriksen flanker task (Eriksen and Eriksen 1974; Botvinick, Nystrom et al. 1999; Bunge, Hazeltine et al. 2002; Ullsperger, von Cramon et al. 2002; Ullsperger and von Cramon 2004; Scerif, Worden et al. 2006; Ullsperger and Yves von Cramon 2006) in which responses to a central cue, e.g. an arrow instructing one movement, are delayed if it is flanked by incongruent stimuli, e.g. arrows in the opposite direction **(Fig. 3.1)**. This increase in reaction time is considered to index interference from competing neural responses evoked by cue and flankers in sensorimotor representations, where sensory cues (in this case, arrows) map to motor responses (movement direction) (Eriksen 1995).

Most discussions of this phenomenon consider the reaction time 'cost' as a feature that should optimally be suppressed if subjects are to make rapid responses. In predictable circumstances, simple 'rules' might be applied at early stages of processing to eliminate the effect of competing responses between the central cue and peripheral, irrelevant flankers in the Eriksen task. However, although the cost evoked by flankers is modifiable (Mayr, Awh et al. 2003) it is never to our knowledge completely eliminated, suggesting competition is a robust process or even perhaps hardwired to occur within our nervous systems.

Movement delay, therefore, is the result of competition between alternative responses. But rather than considering this simply as an inevitable cost, the

delay evoked by conflict might actually also be functionally important, allowing selection between competing action choices before the response is made. For an animal, it might be worth paying the penalty of a small increase in reaction time (evoked by such conflict) to ensure that the most appropriate response is made. Even if some potential action choices are often irrelevant, there may be occasions when they represent the best response particularly in natural, unpredictable environments. For example, a sudden change in the luminance of the visual scene may require very different responses depending upon the cause: if it is simply due to shadows cast by clouds we may be able to ignore this and continue with the task at hand, but if it is due to falling masonry or bricks we need to take aversive action rapidly. Here two action plans are potentially in conflict and the brain has to make a decision, based on prior probabilities and accumulating evidence, on which to select. Thus although the competition evoked by flanker stimuli in the Eriksen paradigm are always irrelevant, this would not invariably be the case for stimuli in the real world.

According to this view, therefore, both relevant and irrelevant competing stimulus-response association signals propagate in the brain, mutually inhibiting each other and leading to a reaction time delay. Indeed, many current decision-making models of response choice involve accumulation of evidence, in distributed brain regions, for each competing choice until decision thresholds are reached (Glimcher 2003; Smith and Ratcliff 2004; Rorie and Newsome 2005; Cisek 2007). From this perspective, *competition* between conflicting responses is a crucial process for action selection, analogous to models that propose competition to be a key part of selection for sensory

attention (Desimone and Duncan 1995; Duncan, Humphreys et al. 1997). Of course, the eventual response is likely to be based on the outcome of competition *biased* by many different aspects of an animal's state (e.g., previous experience, reward contingencies, and task-set) as well as changes in the environment (e.g., new information that alters the weight given to a particular stimulus).

From this perspective, different brain regions might play distinctively different roles in situations of response conflict. While some may be the site of competition between responses activated by environmental stimuli, other brain regions might act selectively to enhance or reduce the impact of particular stimuli, for example, by applying 'top-down' mechanisms (Corbetta and Shulman 2002) to reduce the effect of information from flanker locations in the Eriksen task (Casey, Thomas et al. 2000). The eventual reaction time would be the net result of influences on motor output from several brain regions involved in processing stimulus-response associations. One might consider that PPC is involved in selection for action when stimulus-evoked responses conflict, whereas, frontal regions act to modulate the effect of irrelevant stimuli.

To investigate the possible role of the PPC in processing conflicting information for directional motor control, four different groups of subjects with unilateral brain lesions were tested on a modified Eriksen flanker task, with stimuli presented vertically in the midline to remove any confounding lateralised perceptual bias (**Fig. 3.1**).

3.2 Methods

3.2.1 *Participants*

Patients were recruited from stroke and neurological units with local ethics committee approval. Initially we tested 7 stroke patients with neglect and damage in the angular gyrus of the PPC (mean age: 64, range: 41-78). This is the **PPC neglect** group. Then we recruited three control groups: 7 neglect stroke patients without damage in the angular gyrus of the PPC (mean age 66 range (36-67) which we refer to as the **non-PPC neglect** group, 7 **non-neglect** right brain damage controls (mean age 62, range 31-80; 2 tumour excisions; 5 stroke) and 7 stroke patients with **left hemisphere** damage (mean age 59, range 44-68); see **Table 3.1** for patient demographics. All subjects with right hemisphere stroke used their right hands to perform the task and those with left hemisphere stroke used their left hands as some has patients had contralesional hemiparesis.

Fourteen age-matched normal control subjects completed the conflict task using their right hand (mean age 57.8 range 23-76). Subsequently, 8 further normal controls performed the task using their left hands to act as controls for the left hemisphere patients who also used their left hands due to the high incidence of right hemiparesis. All subjects tested were right-handed and gave written consent according to the Declaration of Helsinki.

3.2.2 *Behavioural assessments*

Visual neglect was assessed using a battery of tests (Malhotra, Greenwood et al. 2004). All patients diagnosed with neglect showed behavioural neglect in

everyday activities and also showed neglect on the Bells cancellation task and/or line bisection on 17 cm lines. Neglect was identified by rightward asymmetry of 3 or more targets found on Bells cancellation task or a rightward line bisection deviation of 5mm or more.

3.2.3 *Apparatus and stimuli*

Subjects moved a custom-built Traxsys (Ringwood, United Kingdom) desktop joystick with a 6cm pole. The position of the joystick was polled every 10ms. The joystick was fitted with a spring which automatically centred the pole. Deadspace was 1% of total movement (0.45 degrees). Stimuli were presented in the vertical midline using Presentation (Albany, USA) software onto a Sony Vaio laptop (PCG-5A1M) for 200ms (**Fig. 3.1**). Interstimulus interval was 2s after initiation of the response. Arrow stimuli were designed so that the directional information would be available to patients even if they had a hemianiopia or object-based neglect; each arrow comprised two chevrons pointing in the same direction and subtended approximately 3 x 2 degrees visual angle. Neutral cues comprised the arrows rearranged so that they carried no directional information; they formed a square (**Fig 3.1**).

Table 3.1 Clinical information for patients performing modified Eriksen flanker task

	Age (years)	Time since stroke (months)	Bells R-L Cancellation score	Line bisection (mm to the right)
PPC Neglect right hemisphere				
	73	94	4	24
	78	1	14	20
	41	0.1	3	5
	66	0.1	1	6
	41	0.3	13	0
	42	0.2	4	9
	64	0.3	5	8
Medians:	**64**	**0.3**	**4**	**8**
Neglect non-PPC right hemisphere				
	36	0.2	0	7
	67	1.8	4	22
	66	0.1	10	7
	64	0.2	7	7
	66	0.3	3	4
	66	0.7	4	10
	64	0.8	14	4
Medians:	**66**	**0.3**	**4**	**7**
Non-neglect right hemisphere				
	74	0.7	-1	-4
	31	0.1	0	0
	62	1	-1	-1
	70	0.2	0	0
	53	0.3	1	-2
	80	0.6	1	0
	57	60	0	2
Medians:	**62**	**0.3**	**0**	**0**
Left hemisphere				
	68*	26	-2	1
	58*	1	0	9
	69*	24	-2	-2
	34	28	1	-4
	68*	90	-1	-2
	64	0.3	0	0
	62	25	-2	-2
Medians:	**64**	**25**	**-1**	**-2**

* = evidence of significant apraxia on copying gestures or miming actions

3.2.4 *Conflict task*

Subjects sat at approximately 100cm from the 15" laptop display and were required to move the joystick as fast as possible leftward or rightward in response to centrally placed arrows. Above and below the target arrow were flankers (separated from target arrow by approximately 3 degrees) which were congruent, incongruent or neutral (**Fig. 3.1**). The stimuli were randomly presented with the constraint that each condition appeared the same number of times per block. There were 8 blocks each containing 24 trials giving a total of 32 trials per condition. A short practice session (< 2mins) took place before the start of the first block.

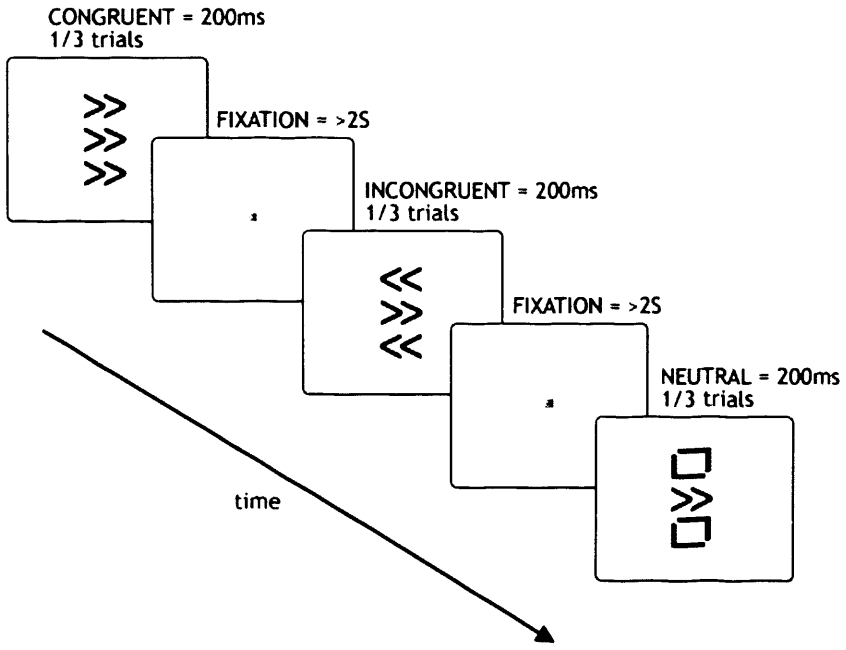


Figure 3.1 Directional Eriksen Flanker task using vertical arrays

Subjects made a speeded response left or right using a small joystick placed centrally. Central arrows were flanked by arrows in the same (congruent) or opposite (incongruent) direction or by squares (neutral condition). The order of stimuli was pseudorandomised with the constraint that the same number of each condition occurred in each block. After each response, there was a delay of 2 seconds before the next stimulus was presented ensuring that the interstimulus interval was at least 2s.

Subjects were instructed to keep their gaze on the laptop display and eye position was monitored by the experimenter. It was explained that there were no visual targets for them to aim for and that they should move the joystick as quickly as possible to its end-stop (25mm lateral movement).

3.2.5 *Data analysis*

Initially RTs in 6 conditions were compared (incongruent, congruent and neutral flankers for rightward and leftward movements) in neglect PPC patients and normal controls. Median RTs were used as reaction time data tended to be positively skewed particularly in the patient groups. This limited the amount of data trimming to only response times less than 200ms (anticipations) and greater than 1500ms; responses with these RTs were excluded from any part of the analysis. The higher boundary was greater than 3 standard deviations away from any individual's average reaction time and reflected trials where the subjects had failed to respond without instruction. The programme was designed to move into the next trial only after a response from the subject to ensure that the patients were alert throughout.

Congruent and incongruent RTs were compared to neutral RTs and expressed as a cost or benefit which was then converted to proportion of the neutral RT to account for differences in response time between the groups, i.e. (median incongruent RT minus median neutral RT)/median neutral RT). Repeated measure ANOVAs were performed separately on the cost/ benefit data which fulfilled criteria for parametric statistics (response direction as a within subject factors and subject group as a between subject factor). In order to investigate

the nature of leftward movement slowing, directional hypokinesia, paired sample t-tests comparing leftward and rightward median RTs for each condition in each group were carried out. Since all PPC neglect patients appeared to perform faster in the right incongruent condition, a single-sample t-test was performed on the incongruence cost data with zero as the reference sample to see if there was significant facilitation within this group.

Error data were not normally distributed and therefore nonparametric statistics were used for the analysis. Friedman test was applied to the proportion of errors for leftward and rightward movements in congruent, incongruent and neutral conditions. In addition we calculated an error cost of incongruence analogous to the RT cost of incongruence described above for leftward and rightward movements ((error $_{incon}$- error $_{neu}$) / error $_{neu}$). Since several subjects made no errors, in order to carry out this calculation, the data were transformed by adding a single extra trial considered to be half error and half correct (Snodgrass and Corwin 1988); the total number of trials in each condition was increased by 1 (approximately 3%) and the total number of errors was increased by 0.5 (approximately 1.5%).

Since we were concerned to rule out the possibility of significantly increased error rate selectively for the right incongruent condition in patients with PPC neglect, uncorrected Wilcoxon signed rank test was performed on the error data despite the risks of obtaining a false positive result. This showed no suggestion of a directional difference and even when incongruent – congruent errors are considered ((error $_{incon}$- error $_{con}$)/ error $_{con}$), there is no difference between left

and right errors rates within the PPC neglect groups (Wilcoxon signed rank score 0, p=1).

Similar analyses were carried out for each control group. Repeated measures ANOVAs were used to compare each control group to the PPC neglect group and a subsidiary analysis compared the controls groups to the age-matched control group. Further t-tests were used to investigate specific hypotheses regarding directional speed differences.

3.2.6 *Lesion plotting*

Lesions were plotted from routine clinical CT or MR scans (18 MR, 10 CT) onto a standard CH2 template using MRICro software available at www.mricro.com. Overlays and 3D renderings were carried out in MRICron (www.sph.sc.edu/comd/rorden/mricron/) after conversion of ROIs to VOIs. Permuted Brunner-Munzel rank order statistic was performed on the right incongruent cost and lesion data for the whole stroke group using MRICron software and non-parametric mapping (NPM for windows also available mricron website). Only areas affected in at least 3 individuals were included in the analysis. Bonferroni corrections were performed automatically using the MRICron NPM software. Further lesions analyses again used the Brunner-Munzel rank order statistic and all 21 stroke patients, but different behavioural data; left incongruence data (Left incongruence cost)*(-1) was used as a measure of general susceptibility to incongruence and (Left –right median RT)*(-1) for each individual was the index used for investigation of leftward movement slowing. Lesion volume was estimated using MIPAV software (Centre for Information Technology, Bethesda, Maryland). Lesion volumes

were then compared between groups using independent samples t-tests and correlated with behavioural performance where appropriate.

3.2.7 *Visual distraction by neutral flankers – subsidiary experiment*

Since the neutral flankers were visually different from the arrow stimuli, we conducted a further experiment to look for the effects of neutral flankers on RT in six normal subjects. The setup was exactly as for the conflict paradigm except that either left or right target arrows were presented alone (2/3 of trials) or in association with neutral, square flankers (1/3 of trials). The proportions were chosen to mimic exactly the proportion of neutral trials in the conflict experiment. 300 trials in total were performed (50% right. 50% left). RTs were compared in the no flanker and the neutral flanker conditions.

3.3 Results

Using a central joystick, subjects made a speeded response leftward or rightward to a central target arrow flanked vertically either by congruent or incongruent arrows, or neutral shapes **(Fig. 3.1)**. The incongruent flanking arrows are normally considered to activate competing motor plans thereby causing a delay in response initiation. In this task, the neutral cue consisted of a square symbol (made up of two of the arrows used as direction cues, but rotated so they no longer carried any directional information). Seven patients with neglect, all with damage to the angular gyrus of the right PPC, were tested **(Fig. 3.2 and Table 3.1)** along with 14 age-matched controls. All subjects were right-handed and used their right hands to perform the task.

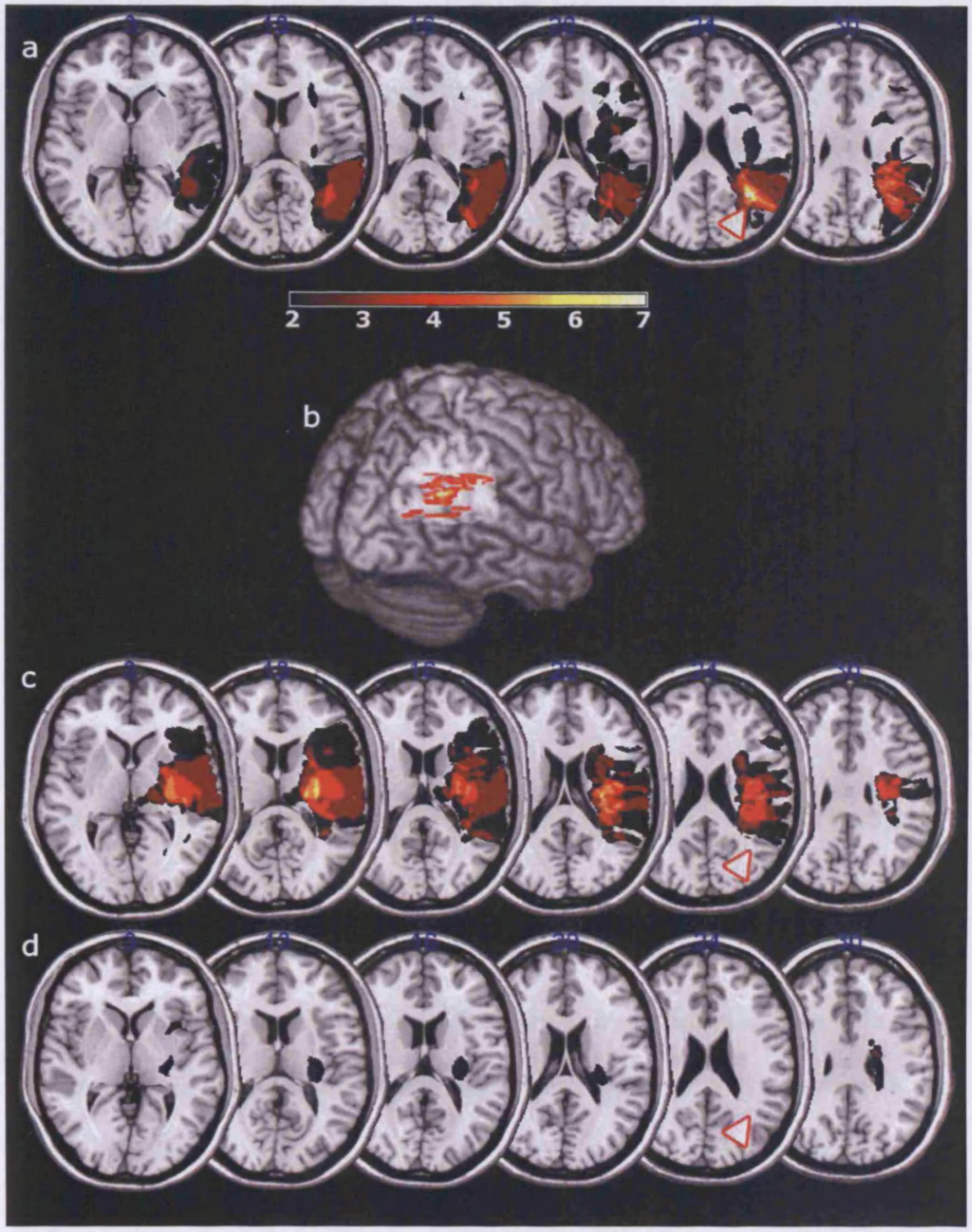


Figure 3.2 Comparison of lesion overlay for PPC, non-PPC neglect groups and right brain damage stroke controls.

Area of maximum overlap in **Neglect PPC** group in the angular gyrus shown both on axial in axial slices (a) and 3 D rendering (b).

Neglect non-PPC patients had more anterior damage with a focus of overlap in the insular and inferior frontal white matter (c).

Patient without neglect **(non-neglect)** had significantly smaller lesions and they were more scattered throughout the right hemisphere (d). The white arrow head with red border points to the area of maximum overlap for the **PPC neglect** patients for comparison. Areas where two or more patients are affected are shown.

3.3.1 *Facilitation for rightward movement in PPC neglect patients under response conflict*

In stark contrast to the performance of normal subjects, the neglect patients with PPC damage were actually faster in the incongruent (conflict) condition than the neutral or congruent conditions for rightward movements only **(Fig 3.3a).** Since there is variability in RT between the two groups, we calculated a corrected cost ((Incongruent RT- neutral RT)/neutral RT) for each direction in each subject **(Fig 3.3b)**. Repeated measures ANOVA on the cost data for these two groups revealed a significant interaction between side and group ($F(1,19)=9.031$, $p<0.01$). One sample t-test on the incongruence cost data for rightward movements of the PPC neglect group confirmed that was significant facilitation (speeding) in the right incongruent condition ($t=3.226$, $p<0.05$).

Thus both groups – healthy controls and PPC neglect patients – had a cost for leftward movements on incongruent trials, but this cost in the conflict condition was lost in the PPC neglect patients for rightward movements. In fact, all patients with PPC damage were actually faster to move rightward when the flankers pointed leftward than when they were neutral, i.e., they had rightward incongruence *facilitation* rather than the normal cost in the conflict situation **(Fig 3.3b)**. Importantly, response times to congruent and neutral flankers did not differ significantly in either direction, for either group. However, it is interesting to note that normal subjects had significant asymmetry in their leftward and rightward incongruence costs (paired t-test $t=3.21$, $P<0.05$). This suggests an asymmetry in conflict processing in the normal brain and this is investigated further in **Chapter 6**.

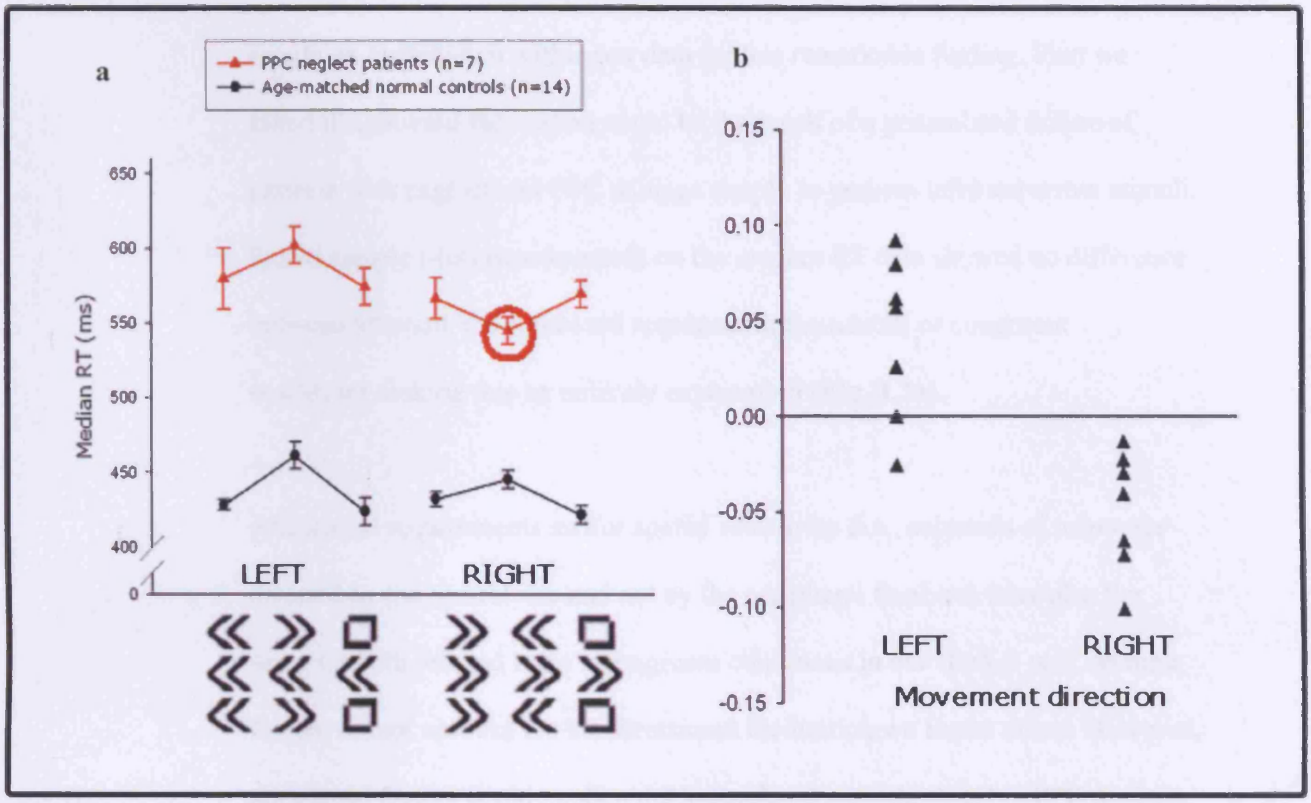


Figure 3.3 Median response times for PPC neglect patients and age-matched normal controls (a) and corrected costs of incongruence (conflict) for all PPC neglect patients (b)
Age-matched normal subjects show a reaction time cost in the incongruent (conflict) condition for both leftward and rightward movements. However, patients with PPC damage and neglect were all faster to move rightward in the incongruent condition than when the flankers are neutral or congruent. Interestingly, normal subjects have a lower incongruence cost for rightward than leftward movements, suggesting an asymmetry of conflict processing in the normal brain.

Every patient with PPC damage and neglect was faster to move right when the flanker were incongruent than when they were neutral (or congruent – not shown here (b)). All but one of the patients had a cost of incongruence for leftward movements. The one patient with facilitation for leftward movements had an unusual multifocal lesion due to carotid stenosis, but since it involved the right PPC and there was no evidence of any left hemisphere damage, he was included in the analysis.

To our knowledge, no previous flanker study has shown speeding in the incongruent condition compared to neutral, in any subject group. We therefore sought an explanation within our data for this remarkable finding. First we asked if rightward facilitation could be the result of a generalised failure of patients with neglect and PPC damage simply to process leftward arrow stimuli. Paired sample t-test (uncorrected) on the median RT data showed no difference between leftward and rightward responses in the neutral or congruent conditions making this an unlikely explanation **(Fig. 3.3a)**.

Attentional requirements and/or spatial selectivity (i.e., selection of responses directed by the central cue and not by the peripheral flankers) were also the same for both left and right incongruent conditions in our flanker task, so these factors cannot account for the directional facilitation we found either. However, attentional factors could explain the generalized slowing found in PPC neglect patients even though they were using their spared, ipsilesional arm **(Fig 3.3)**. Such generalized slowing is a well described finding particularly in patients with right hemisphere damage and may relate to failure of non-lateralized sustained attention (Howes and Boller 1975; Husain and Rorden 2003). Finally, note that participants made ballistic movements with the joystick without having to locate a spatially lateralized target. Therefore, pure attentional or visual localization accounts for directing movements to a visual target, also cannot readily explain the directional difference found in our PPC neglect group.

Could a speed-accuracy trade off explain the rightward facilitation we observed in the response conflict or incongruent condition? If this were the case, one would expect that the error rate in the patients would be disproportionately raised in the right incongruent condition. However, this is not what we found. There were no significant differences in error rate between the flanker types in the PPC neglect group (**Fig. 3.4a**). In contrast there were significant difference between conditions in the error rates in the normal control group (chi-square =22.02, $p<0.001$). Healthy subjects made significantly more errors in the incongruent condition, whereas, as a group, the PPC patients show only a non-significant trend towards this tendency with some patients actually demonstrating the reverse effect (i.e., fewer errors in the incongruent condition).

In addition, we investigated a speed accuracy trade-off by calculating an error cost of incongruence analogous to the RT cost described above (see methods). Again there was no suggestion of a raised error rate in the right incongruent condition ($Z=-0.314$, $p=0.753$) **Fig 3.4b**). These error data rule out a speed-accuracy trade off as the cause for the speeded right movement in the incongruent condition. Rather, our data suggest a deficit at the level of motor preparation in PPC neglect patients which manifests when there is conflict between possible action plans.

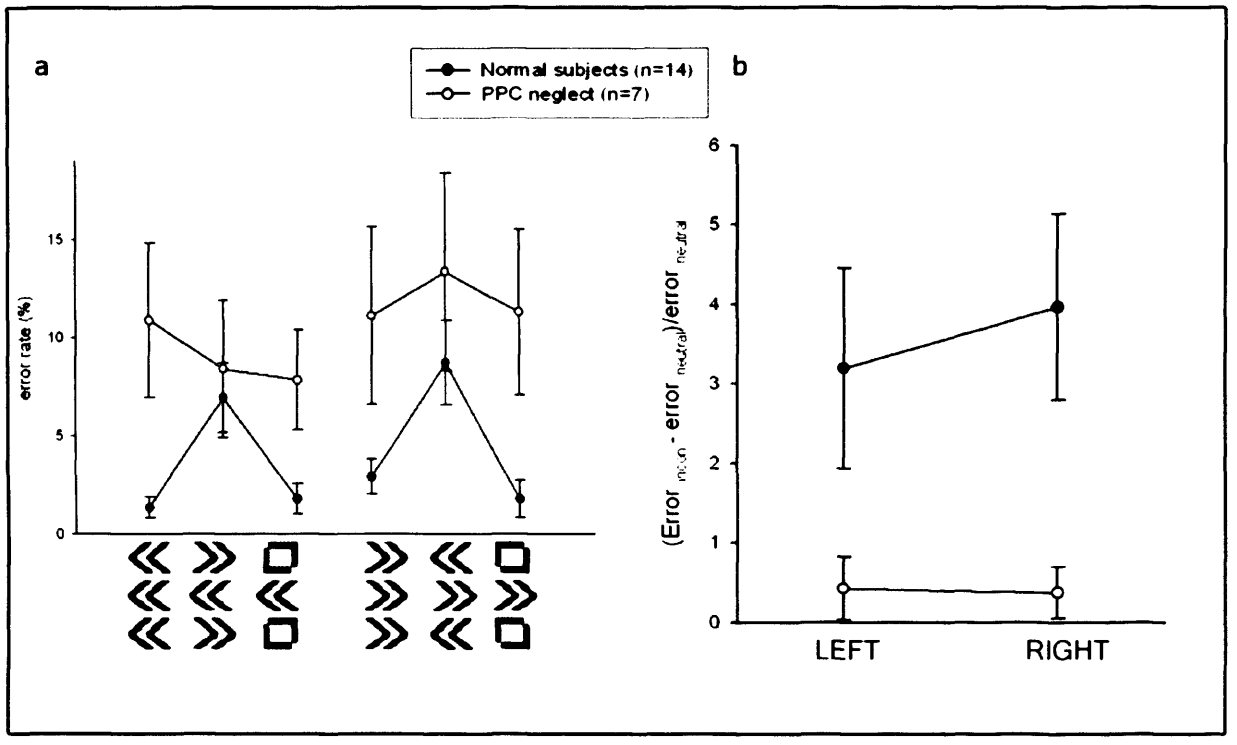


Figure 3.4 Error rates in normal control subjects and PPC neglect patients

a) Normal subjects have increased errors in the incongruent condition. Even when the error cost of incongruence is calculated (b), there is no trend for right PPC neglect patients to show an increased error rate for rightward incongruent compared with leftward incongruent movements. Note that although error rates appear higher in the right than left incongruent condition, this effect is not consistent, with 3 of 7 PPC neglect subjects showing the reverse pattern.

Can rightward facilitation when there is such competition between actions plans also account for any directional motor deficit – directional hypokinesia (DH) – in PPC neglect patients? Note that in our group, there was no *directional* slowing in response initiation in either neutral or congruent conditions (**Fig 3.6** and see above). However, these patients were significantly faster to move right than left only in the incongruent, conflict condition ($t=4.115$, $p<0.01$). These findings show that directional motor asymmetry occurs in patients with PPC damage and neglect selectively when there is competition between alternative responses. Importantly, this DH results *not* from leftward slowing but from rightward facilitation under situations of response conflict.

Next, we investigated whether rightward incongruence facilitation occurred only in neglect patients with right PPC damage. To do this, three further control groups were recruited. Right hemisphere stroke patients with neglect but without damage in the angular gyrus (**non-PPC neglect**, n=7) were tested to establish whether or not rightward incongruent facilitation occurred in all patients with neglect, or was lesion-specific. We examined a second control group, this time **non-neglect** right hemisphere patients (n=7), to see if deficits were neglect-specific.

Finally, **left hemisphere** patients (n=7), with or without parietal damage, were assessed to explore whether there were analogous abnormalities following left PPC damage.

3.3.2 *Neglect patients without PPC damage have increased conflict costs*

Seven right hemisphere patients with neglect, but without any damage within the angular gyrus were tested **(Table 3.1)**. The area of maximum overlap for this patient group was within the white matter of the inferior frontal gyrus and insula **(Fig 3.2c),** distinctly different from the previous PPC neglect group. Apart from lesion location, **non-PPC neglect** patients were well-matched with the PPC neglect group in terms of age, lesion volume and severity of neglect (independent samples T-tests showed no significant difference between the two groups). Performance on the flanker task revealed that these **non-PPC neglect** patients *did* incur a cost of incongruence for rightward movements, unlike PPC neglect patients **(Fig 3.5)**. Repeated measures ANOVA on the cost data for **non-PPC neglect** and the **PPC neglect** patients showed a significant interaction of group and side ($F(1,12)=16.223$, $p<0.005$). The non-PPC neglect patients also differed significantly from normal controls in that they had a greater intrusion by incongruent flankers onto performance that was similar for both leftward and rightward movements (Between subjects effect: $F(1,19)=5.891$, $p<0.05$; **Fig. 3.5**).

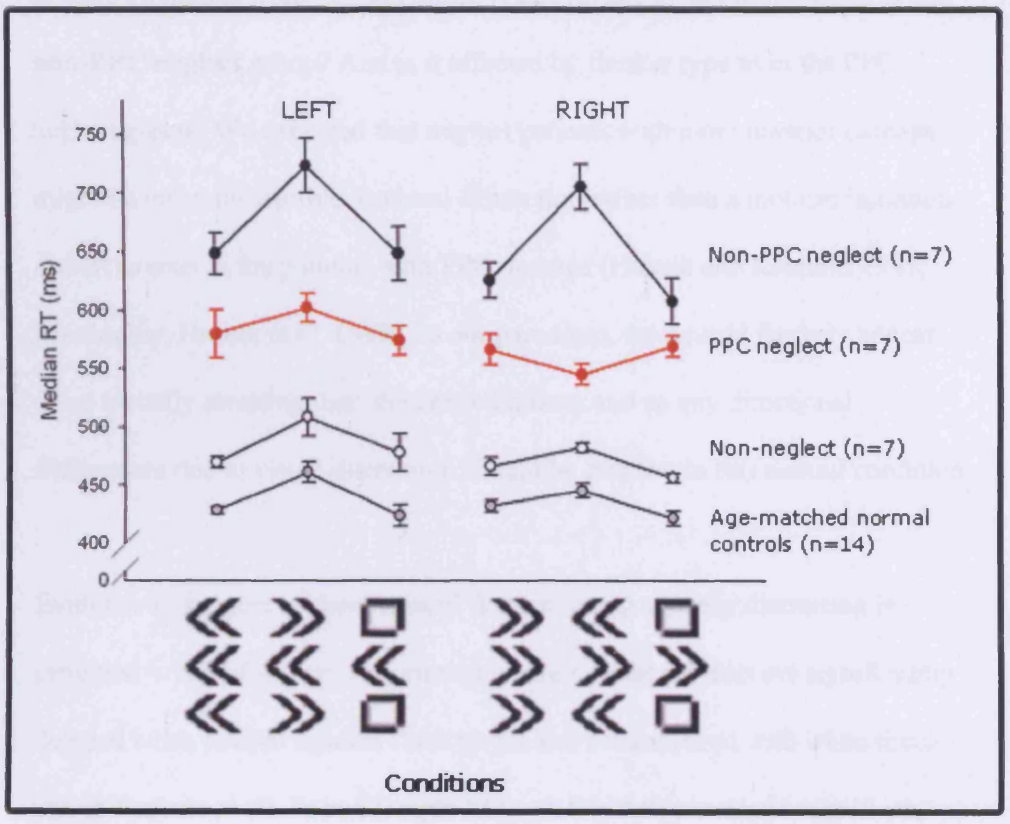


Figure 3.5 Reaction times across conditions
All groups showed a reaction time cost in the incongruent (conflict) conditions for both leftward and rightward movements, except the PPC neglect group who demonstrated facilitation (faster RTs than neutral) in the conflict situation for rightward movements only (when the rightward cue was flanked by leftward arrows).

Is there directional response asymmetry, directional hypokinesia (DH), in this **non-PPC neglect** group? And is it affected by flanker type as in the PPC neglect group? We expected that neglect patients with more anterior damage might be more susceptible to visual distraction rather than a motoric initiation deficit as seen in the patients with PPC damage (Husain and Kennard 1997; Mattingley, Husain et al. 1998). In our paradigm, the neutral flankers appear more visually arresting than the arrow flankers and so any directional differences due to visual distraction should be greatest in this neutral condition.

Evidence in support of these neutral flankers being visually distracting is provided in the subsidiary experiment where normal subjects are significantly delayed when neutral squares flank target arrows compared with when there are no flankers at all. Paired sample t-test on this data revealed a significant delay in the neutral compared with the no flanker condition ($t=4.7$, $p<0.005$). The average delay was 15ms with 4 of the 6 subjects having a within-subject significant delay in the neutral flanker condition.

Non-PPC neglect patients were significantly slower to move left than right only in the neutral condition (paired sample t-tests of leftward and rightward median RTs : $t = 4.761$, $p<0.005$; **Fig 3.6).** Therefore, **non-PPC neglect** patients were particularly susceptible to this distraction when planning a leftward movement. Taken together, the results suggest there might be two distinctly different forms of DH or motor initiation deficit: **PPC neglect** patients have relative facilitation of rightward movements during conflict, whereas **non-PPC neglect** patients with more frontal lesions demonstrate DH

in the neutral, most visually distracting condition, with slowing of leftward movement initiation.

Given that in this **non-PPC neglect** group there were significant differences between left and right RTs in the neutral condition, a subsidiary analysis was performed to ensure that the bilateral difference in incongruence cost found between these PPC neglect patients and normal subjects was independent of directional difference in the neutral RTs. To do this we again calculated a cost of incongruence for each subject, but this time using the congruent RT as baseline ((Incongruent-congruent RT)/congruent RT) as leftward and rightward congruent RTs did not significantly differ. Again there were significant between group differences across both left and right movements ($(F(1,17)=6.1$, $p<0.05$: average cost normal subject = 5.2% (SE 1.5%) vs non-PPC neglect = 14 % (SE 2.8%)) and no significant interactions with direction of movement.

3.3.3 *Patients without neglect have normal response costs in the flanker task*

Next we ask if right hemisphere patients without neglect have either reduced or increased costs of incongruence. Seven further right hemisphere patients were tested, now with no evidence of neglect either in terms of symptoms or performance on standard clinical tests **(Table 3.1 and Fig 3.2d)**. As with all other control groups, **non-neglect** patients did not show facilitation by conflict for rightward movements (repeated measures ANOVA on the cost

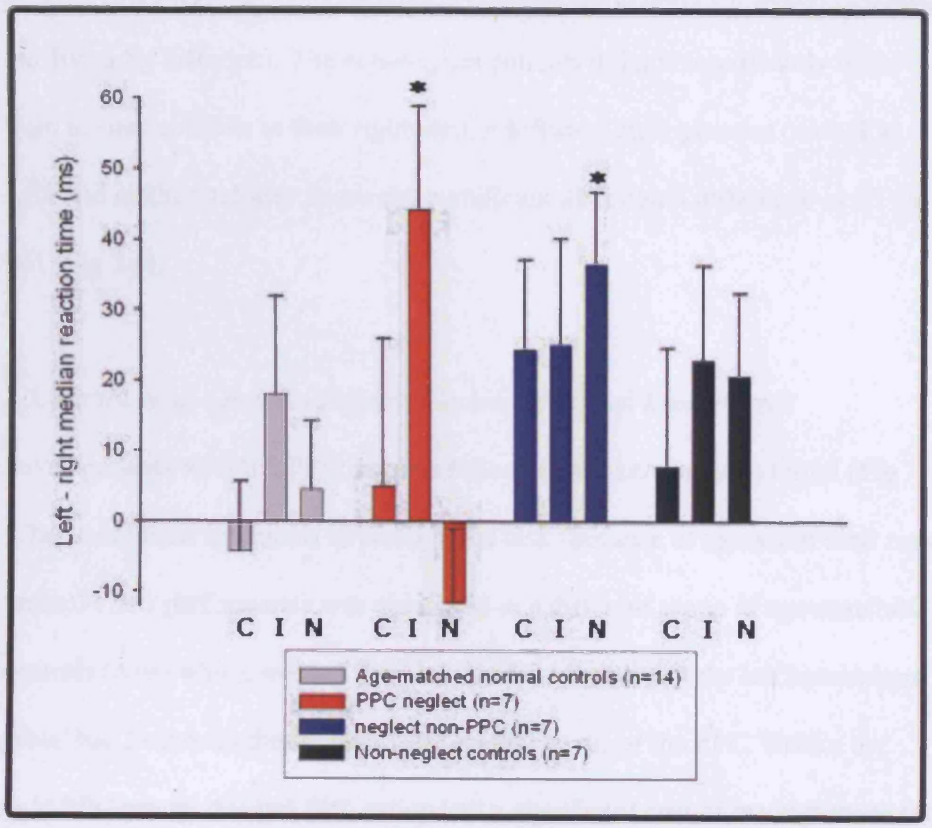


Figure 3.6 Directional hypokinesia for each flanker condition
PPC neglect patients were significantly slower to move left than right, but only in the incongruent condition when there are competing motor plans. **Non-PPC neglect** patients were significantly slower to move left than right, but only in the neutral condition which was visually most distracting. **C:** congruent; **I:** incongruent; **N:** neutral.

data for PPC and non-neglect patients revealed a significant interaction of group x side ($F(1,12)=4.895$, $p<0.05$) revealing again that PPC neglect patients are distinctly different). The non-neglect patients did not significantly differ from normal controls in their rightward or leftward incongruence costs **(Fig 3.5)**, and neither did they show any significant directional difference in RT or DH **(Fig 3.6)**.

3.3.4 *Is there an equivalent effect of lesions of the left hemisphere?*

Seven patients with left PPC damage following stroke were also tested (**Fig 3.7a**) using their left hands to perform the task (because of paresis of their right limbs). Their performance was compared to a different group of age-matched controls (n=8) who also used their left hands. All seven of the left hemisphere group had lesions in the region of the angular gyrus of the PPC. Unlike the right PPC group, this left PPC group had a significant cost of incongruence for both leftward and rightward movements **(Fig 3.7b)**. Repeated measure ANOVA comparing the incongruence costs data from these left hemisphere patients with that of age-matched controls using their left hand showed no significant difference between the groups. Thus patients

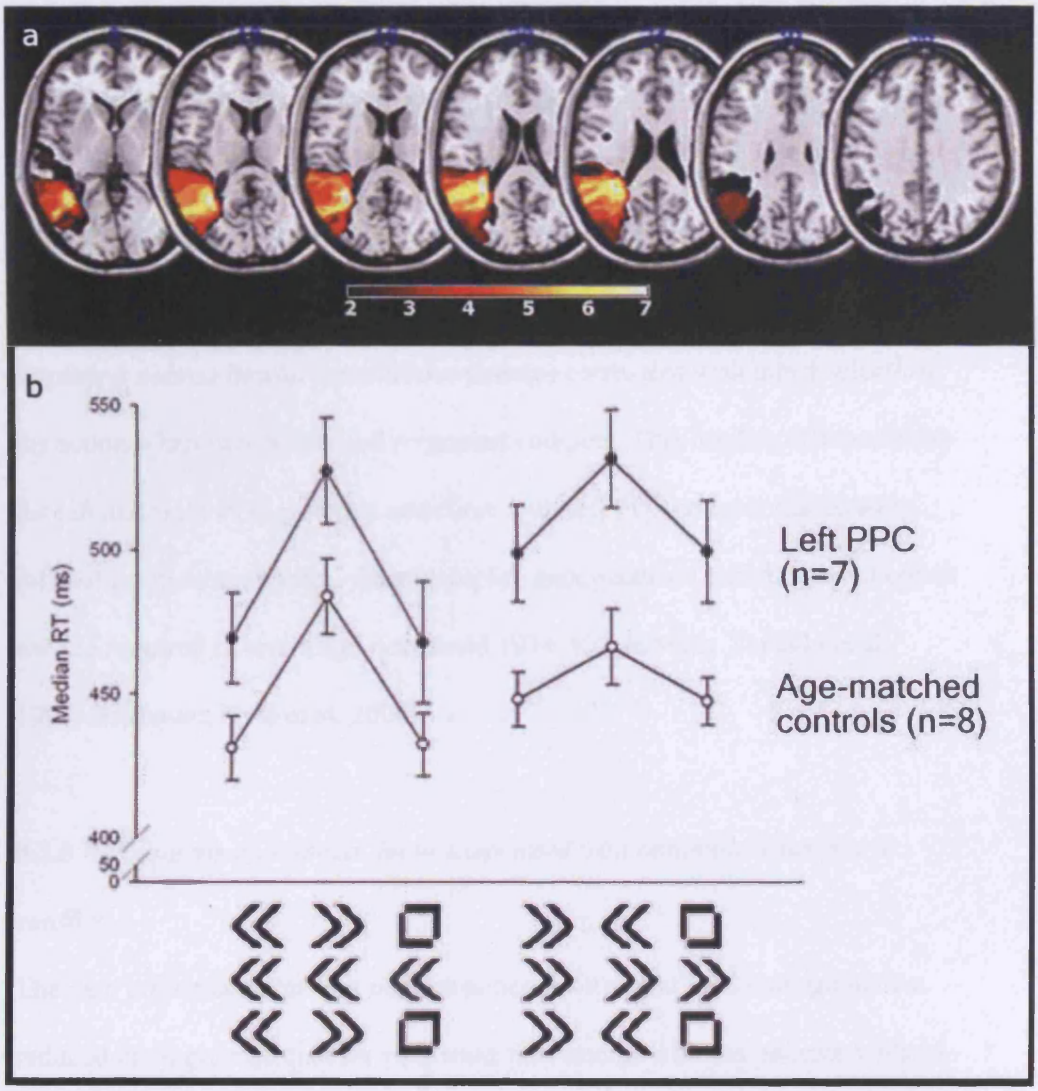


Figure 3.7 Lesion overlay and behavioural performance for left hemisphere patients. Three of the subjects had damage in the angular gyrus of the left PPC (a). Left hemisphere patients were slower in the incongruent condition for both leftward and rightward movements (b).

with left PPC damage do not show the analogous deficit to those with right PPC damage when processing response conflict.

Four of these seven left PPC patients had apraxia when tested clinically suggesting motor control deficits within the group (**Table 3.1**). Yet they displayed normal flanker interference patterns consistent with intact selection for action when two directional responses compete. This implies different roles for left and right PPC in action selection, with left PPC patients manifesting difficulties in motor control when complex manipulations and functional object use are required (Kimura and Archibald 1974; Kawashima, Yamada et al. 1993; Buxbaum, Kyle et al. 2006).

3.3.5 *Refining the anatomical locus associated with abnormal response to conflict*

The data presented show that neglect patients with right PPC damage have a reduced incongruence cost for rightward movements whereas patients without damage in the PPC tend to have increased RT slowing when movement cues conflict. Lesion overlap maps such as those in **Fig 3.2** do not differentiate between loci of damage associated with abnormal behavioural performance and those areas most likely to be damaged by vascular insult in a particular territory.

Therefore to investigate further the precise brain regions damaged in patients with a low rightward incongruence cost (or facilitation), a permuted Brunner-Munzel rank order analysis was performed on the continuous right

incongruence costs combining data from all 21 right hemisphere patients (**PPC neglect**, **non- PPC neglect** and **non-neglect**; **Fig 3.8a**). The advantages of using the Brunner-Munzel rank order statistic are, first, that it is robust in the face of violations of normality and, second, the use of a continuous dataset containing all three of our right hemisphere groups meant division of group according to either lesion location or behaviour was not required prior to running the statistic (Rorden, Bonilha et al. 2007). Therefore this test provides a relatively assumption-free measure of whether or not damage at each voxel is associated with a reduced right incongruence cost (or facilitation by conflict).

Only voxels where 3 or more subjects had lesions were tested. Even after Bonferroni correction for multiple comparisons, right angular gyrus was the only area highly significantly associated with a low/negative rightward incongruence cost **(Fig 3.8a and b)**. The most affected area lay within the cortex of the right angular gyrus reaching a Z score of 45, with Z scores of >4.62 indicating a highly significant association with low rightward incongruence cost. This region of angular gyrus is just inferior to the intraparietal sulcus where neurons coding motor intention have been reported in monkeys (Andersen and Buneo 2002; Stoet and Snyder 2007). However, activations within the angular gyrus in humans during response conflict have been shown in fMRI studies (Botvinick, Nystrom et al. 1999; Liston, Matalon et al. 2006). This discrepancy may reflect differences between human and monkey PPC. An alternative explanation is that the area

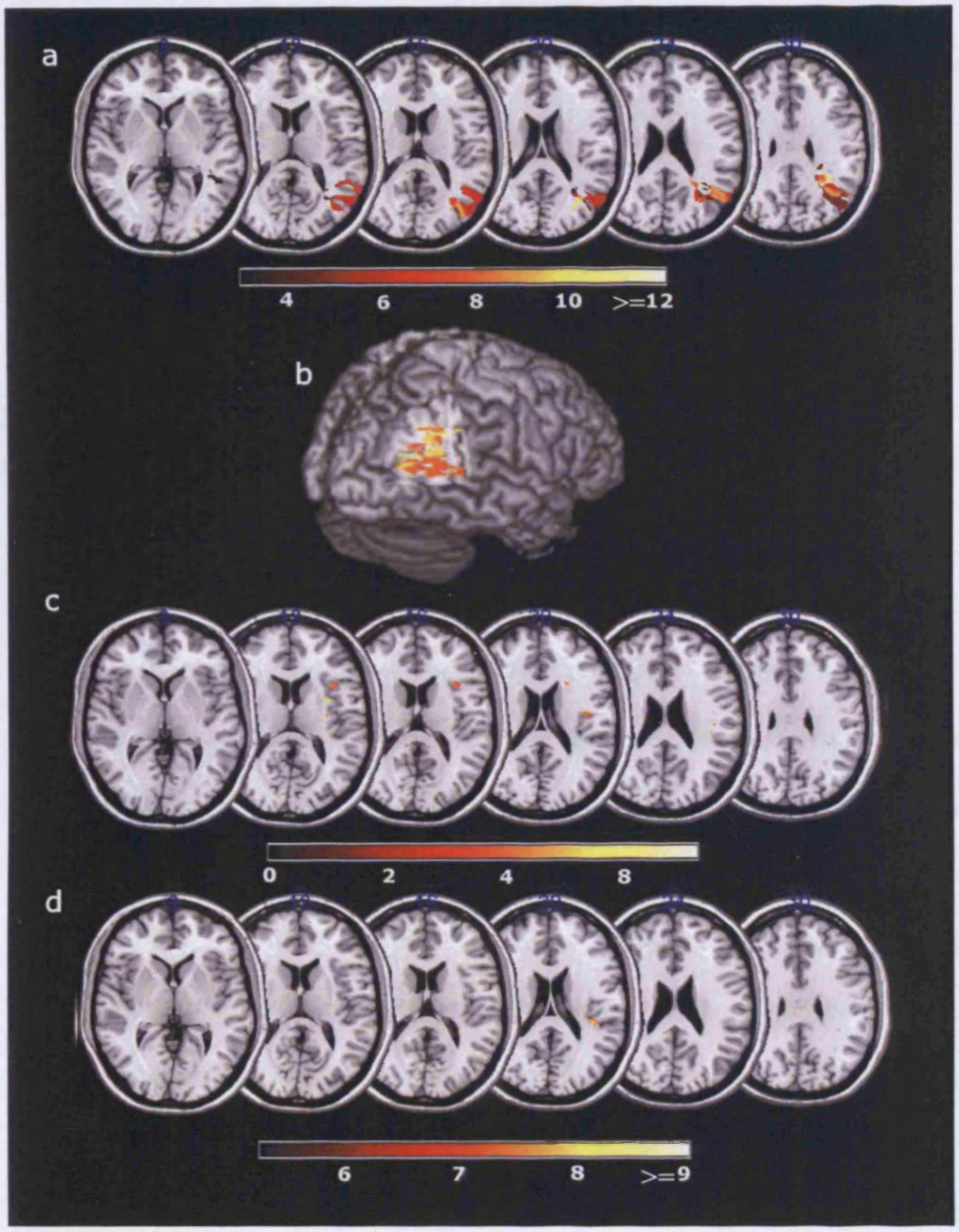


Figure 3.8 Lesion loci associated with abnormal performance

a) Damage to right angular gyrus was highly significantly associated with a reduced incongruence cost (facilitation). The highest Z score is 45 (MNI coordinates of this area of damage: 38, -55, 24). Z scores over 4.62 are significant after Bonferroni correction at $p<0.05$ level.
b) Three-dimensional rendering of the overlay showing the locations of areas significantly associated with a reduced or negative incongruence cost.
c) Right insula and inferior frontal gyrus damage significantly correlate with increased *left* incongruence cost. The highest Z score is 6.55 (MNI coordinates of this area of damage: 34, 14, 20). Z scores>4.62 are significant after Bonferroni correction at $p<0.05$ level.
d) Lesions of the right insula are significantly associated with leftward directional hypokinesia (black circle). The highest Z score is 9.05; MNI coordinates of this area of damage: 34, -18, 20. Z scores>4.62 are significant after Bonferroni correction at $p<0.05$ level.

identified in our analysis also includes white matter fibres, whose origins may include the intraparietal sulcus.

Using the Brunner-Munzel rank, we next asked whether there was a brain region which when damaged rendered subjects more susceptible to irrelevant, competing stimulus-response activations, i.e. greater costs during conflict. We have already seen that a *reduced* right incongruence cost associates with PPC damage. Because all subject groups shared a positive conflict cost for leftward movements we used the *left* incongruence data as a general measure of susceptibility to conflict. Again all right hemisphere patients' scans were assessed (21 in total) and voxels affected in three or more individuals were probed to see if they were associated with a high leftward incongruence cost **(Fig 3.8c and d)**. Brunner Munzel analysis revealed that anterior insula and inferior frontal white matter were both significantly more likely to be affected in those with an increased incongruence cost, again even after Bonferroni correction. The maximum Z score of 6.55 occurred in the inferior frontal gyrus (Z scores > 4.62 being significant). Thus damage to these frontal areas was associated with greater reaction time costs in situations of response conflict.

Lesion volume was also assessed as a possible predictor of patient performance. Lesions in the two neglect groups were larger than in the non-neglect group (mean volumes: PPC neglect vs non-PPC neglect vs non-neglect = 9920 mm3 (SE 3515) vs 12024 (SE 2814), vs 2585 (SE 601)). However, behavioural performance did not correlate with lesion volume either for the right incongruence cost (when all patients are tested together spearman's rho = 0.179,

p=0.439 or when just PPC neglect and non-neglect patients are compared spearman's rho = -0.446, p=0.110) or for the left incongruence cost (all patients spearman's rho = 0.123, p=0.594).

3.3.6 *Which brain areas are associated with leftward slowing – directional hypokinesia?*

Thus far the analyses have identified two types of DH: the first is relative DH due to rightward *facilitation* during conflict; the second DH due to leftward *slowing*, occurs when flankers are *neutral* suggesting that it is due to visual distraction while movement planning. Both conventional lesion overlap analysis **(Fig. 3.2a)** and Brunner-Munzel rank order analysis **(Fig. 3.8a)** show that the first type of DH is associated with right angular gyrus damage. The final lesion analysis aimed to identify areas of brain most likely to be damaged in any of the 21 right hemisphere patients who showed the second type of DH, reflected by a *slower* RT for leftward compared to rightward movements when flankers were *neutral*. Note this is different from the analysis which examined brain areas associated with increased costs for leftward movements in the left *incongruent* condition (i.e., **Fig. 3.8c,d**).

We ran a Brunner Munzel rank order analysis, this time using the ((LEFT neutral RT) minus (RIGHT neutral RT))X(-1) as a measure of leftward slowing for each of the 21 subjects with right hemisphere damage. Even after Bonferroni correction, the area most associated with leftward directional slowing in the neutral condition was the right posterior insula **(Fig 3.8d)**. The highest Z score was 9.05 (significance reflected by Z >4.62). Therefore

subjects with damage in the insula are significantly more susceptible to distraction from neutral flankers when planning leftward compared to rightward movements. Thus both conventional behaviour-lesion overlap correlation within each group and analyses performed on the combined data sets across all our right hemisphere patients provide a consistent pattern of results for this complex data set.

3.4 Discussion

Used a modified Eriksen flanker task, with all stimuli presented in the vertical midline, the effect of unilateral lesions on processing conflicting directional cues was investigated. Paradoxically, patients with neglect following right PPC damage were actually *faster* in the incongruent (conflict) condition than on neutral trials, but only for rightward movements. For leftward responses, they showed the normal pattern of reaction time costs in the presence of rightward flankers (**Fig. 3.3**). To the best of our knowledge, focal lesion studies have not previously identified any brain region which when lesioned leads to direction-specific facilitation, using the Eriksen protocol as a probe of response conflict (Ullsperger and Yves von Cramon 2006). Analogous effects were not observed following left hemisphere (including extensive left parietal) lesions. In contrast neglect patients with right frontal damage were generally much slower and had a disproportionate increase in reaction time in the incongruent condition *bilaterally*. Thus these individuals incur a significantly higher cost during response conflict but this effect is not directionally specific.

How can we account for such a reversal of the RT cost (facilitation) from incongruent flankers in our **PPC neglect** group? Careful analysis of our data excluded several possible explanations. First, we ask if the neglect patients with right PPC damage simply do not process the leftward arrow stimulus normally, i.e., they experienced difficulty recognizing leftward arrows as a signal to move left and therefore took longer to respond. This is made highly unlikely by the finding that when a leftward target arrow was presented centrally with neutral or congruent flankers, these individuals were able to initiate leftward responses with similar latencies to rightward movements. However, this possibility is investigated further in chapter 5 where response conflict is generated without visual cues, in a free choice paradigm.

Next we considered an explanation based on visual attention, e.g., that perhaps **PPC neglect patients had an exaggerated, narrow 'spotlight' of attention on the** central target and thus automatically filtered the flanker information more than normal individuals (Casey, Thomas et al. 2000). However, the attentional requirements were identical for both leftward and rightward movements and it is evident that a cost was incurred in the leftward incongruent condition, but not the right. Since the abnormal finding was unidirectional, an explanation based solely on attention is precluded. Could rightward conflict facilitation in the **PPC neglect** group reflect a spatial deficit for left-sided stimuli? The flanker task was specifically designed to exclude the possible confound of spatial bias: all stimuli were presented in the vertical midline and subjects responded using a central joystick making ballistic movements without needing to identify or localize a lateralised visual target. Therefore, none of these

accounts – perceptual, attentional or spatial – explain these findings, although it is important to stress that this does not mean that abnormalities in each of these domains do not occur in neglect patients.

Thus it appears that direction-specific facilitation in the incongruent condition in **PPC neglect** patients is best explained by a *motoric* deficit that occurs selectively when response plans compete. Specifically, leftward flanker-induced response plans do not appear to be activated commensurately in neglect patients with right PPC damage when they are in competition with a target-induced rightward response plan. Such limited inhibition of rightward movements may effectively lead to over 'impulsivity' towards the right in situations of response conflict in these individuals.

3.4.1 Independent parietal and frontal responses to conflict

But while failure to represent response alternatives in **PPC neglect** patients might explain loss of the incongruent reaction time cost, remarkably, our patients with parietal damage actually showed significant *facilitation* for rightward movements in the presence of leftward flankers, i.e., faster responses than in the neutral condition. To account for the paradoxical facilitation observed in this group, the action of a second system must be involved, this time in the frontal lobe, which is proposed to act simultaneously with the PPC (Botvinick, Nystrom et al. 1999; Carter, Botvinick et al. 1999; MacDonald, Cohen et al. 2000; Botvinick, Braver et al. 2001; Botvinick, Cohen et al. 2004). In this schema, PPC and prefrontal regions interact with premotor or motor

regions to influence response choice and movement initiation when conflicting responses compete for selection **(Fig 3.9)**.

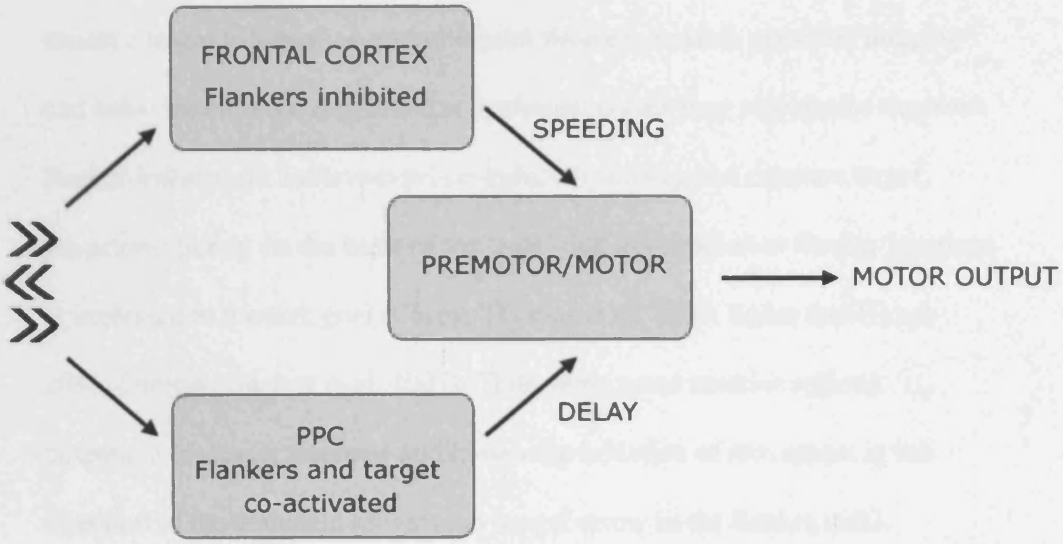


Figure 3.9 Schematic of interaction between parietal, prefrontal and premotor regions in response selection

When two responses conflict such as in the incongruent condition of the Eriksen flanker task, both possible responses (evoked by target cue and flankers) are activated within the parietal lobe. These responses mutually inhibit one another causing response delay. In contrast, the frontal cortex enhances the target and/or inhibits the flankers selectively to speed response initiation. Each of these areas influences the decision threshold reached in the premotor cortex. Damage to the PPC reduces the response delay, but the intact prefrontal cortex still boosts the target response thus producing facilitation observed in our neglect PPC patients.

According to this proposal, part of the response delay in situations of response conflict such as the flanker task is attributable to competition between partially activated stimulus-evoked response associations (for target and flankers) *within the PPC*. In contrast to the parietal role, prefrontal cortex may selectively enhance target information and/or inhibit flankers. Indeed, previous imaging and behavioural work suggests that prefrontal cortex may selectively suppress flanker-induced (or irrelevant prime-induced) activity and enhance target processing purely on the basis of the 'rule' that information at flanker locations is irrelevant to the task goal (Casey, Thomas et al. 2000; Egner and Hirsch 2005; Sumner, Nachev et al. 2007). Thus, these more anterior regions potentiate the target response and hasten the initiation of movement in the direction of the dominant motor plan (target arrow in the flanker task).

Critical to this proposal is the idea that PPC and prefrontal responses are activated *independently* by the stimulus conflict in the environment (target vs. flankers in our experimental situation). In patients with damage to the PPC, the incongruence delay is lost – or at least greatly reduced – because competition between partially activated stimulus-evoked response associations is reduced. But the key point is that prefrontal regions remain intact in these individuals. They therefore continue to enhance the response to the target and/or inhibit that to the flankers, regardless of whether the PPC is 'off-line'. Without any competition in the (lesioned) PPC which normally contributes to the reaction time delay, the net result of such prefrontal activity would be relative *facilitation,* i.e., response times that are faster than neutral, as we observed in our **PPC neglect** patients. Conversely, when prefrontal regions are damaged,

the delay due to competition within the PPC still occurs, but now without the potentiation (speeding) of target responses from more anterior areas. Thus incongruent responses are disproportionately slow as in our neglect patients with anterior white matter and insula damage.

It is evident, however, that the facilitation observed in our right **PPC neglect** group was only for rightward movements (with leftward flankers). Is there a system in the left parietal lobe mirroring processes occurring in the right PPC? Functional imaging studies have demonstrated bilateral parietal activation during response conflict tasks (Bunge, Hazeltine et al. 2002; Cavina-Pratesi, Valyear et al. 2006; Liston, Matalon et al. 2006). However, behavioural data from our left hemisphere patients did not reveal any directional specific facilitation. One possible explanation for this is that the right PPC has a bilateral function in resolving motor competition, whereas, the left hemisphere fulfils a unidirectional role promoting competing rightward movements only. This would be analogous to the bilateral allocation of spatial attention within the right inferior parietal lobe thought to explain the higher incidence of unilateral neglect following right compared with left hemisphere strokes (Heilman and Vandenabell 1980; Mesulam 1981). Therefore, the right PPC compensates to some degree for the loss of the left PPC in our left hemisphere patients, but the reciprocal compensation after right PPC damage cannot occur.

It is important to note that patients with right parietal and frontal lesions are still able to make leftward and rightward movements with the right hand, but that there are distinctly different abnormalities of motor programming in these

two patient groups. The different findings in these groups suggest that, normally, parallel processing streams must be activated and be capable to some extent of independent activity. Recent evidence suggests these processing streams may influence motor output via a final common pathway involving premotor cortex **(Fig 3.9)** where information on action choices accumulates until a decision threshold is reached (Passingham 1993; Cisek and Kalaska 2002; Glimcher 2003; Cisek and Kalaska 2005). Note that although we consider parietal and frontal systems are activated independently by response conflict, we would not suggest that interactions between these systems do not normally occur; clearly, there are massive parieto-frontal connections which mediate such traffic. Our scheme simply proposes that regions within the PPC and frontal lobe may be activated in parallel by response conflict and damage to one system does not preclude activation in the other.

3.4.2 Directional motor deficits in parietal and frontal neglect

Finally we consider the directional motor deficits found in neglect patients and their anatomical localisation, a topic that has been highly controversial (Heilman, Bowers et al. 1985; Bartolomeo, D'Erme et al. 1998; Mattingley, Husain et al. 1998; Mesulam 1999; Bartolomeo, Chokron et al. 2001; Harvey 2004; Coulthard, Parton et al. 2006; Sapir, Kaplan et al. 2007). Slowing of leftward movement initiation – directional hypokinesia – has been reported following both parietal and frontal lesions (Mattingley, Bradshaw et al. 1992; Mattingley, Husain et al. 1998). In our study, we have shown two clear cut patterns of directional hypokinesia, both of which could exacerbate the neglect syndrome. Neglect patients with PPC damage had directional imbalance due to

rightward facilitation only in the incongruent condition when *competing* response plans are activated. Thus the directional deficit in **PPC neglect** was due to *faster* rightward responses (i.e., relative leftward slowing) when there was conflict or competition between motor plans, analogous to models that propose competition to be a key part of selection for sensory attention (Desimone and Duncan 1995; Duncan, Humphreys et al. 1997).

In contrast, neglect patients with damage in the right posterior insular demonstrated directional hypokinesia only in the neutral condition which is most visually distracting, suggesting these individuals struggle to filter the intrusive effects of visual distraction when planning a left compared to a rightward movement. Moreover, the directional hypokinesia in these cases was due to slowing of leftward responses, not speeding of rightward ones as in the PPC patients. Thus the experiments reported here have demonstrated a dichotomy between parietal and more anterior neglect patients in their directional response speeds depending on the context of the instructed movements. This dissociation may explain the heterogeneity in previous studies which have reported patients grouped according to their clinical syndrome without necessarily distinguishing between cases according to their lesion anatomy.

Previous studies of conflict related brain activity have largely focussed on the way the brain acts to minimise intrusion from (unwanted) conflicting information. However, in my view, it is critical for optimal control over behaviour for conflicting information (cueing alternative movement plans) to be processed and evaluated before an action choice is made. Here a system

involving the PPC which activates competing motor plans in response to conflict has been identified and may underlie the response delay observed when we respond to incongruent information. The interaction between this parietal system, which appears to play a key role in competition for action selection, and the prefrontal system, which may limit interference on performance, may be essential for flexible control of behaviour in an environment which presents rapidly changing situations of response conflict.

Chapter 4: Masked priming

4.1 Introduction

In Chapter 3, we propose that patients with PPC damage fail to process competing leftward action plans. Such weak activation of leftward motor programs occurred in patients with neglect and PPC damage. However, while this deficit may exacerbate symptoms of neglect, it may not be neglect-specific. Patients with PPC damage who perhaps have recovered from, or never had, neglect could in theory still fail to propagate leftward motor plans, but the impairment may not be accompanied by other component deficits that lead to manifestation of neglect (Husain and Rorden 2003).

To investigate this further, in this chapter, patients with a range of right-sided brain lesions, with and without neglect, are tested using a masked prime paradigm (see introduction). In this paradigm, briefly presented prime arrows are subsequently masked rendering them imperceptible (Eimer and Schlaghecken 1998; Eimer 1999). Masked primes activate response plans without the directional information reaching visual awareness (Eimer and Schlaghecken 1998; Eimer 1999). Since these prime arrows are not acted upon, one could consider that they induce a competing response program similar to the flankers in the Eriksen flanker task used in chapter 3, but not consciously perceived.

In normal elderly subjects masked primes presented approximately 200ms before a target cue cause a delay if the prime and target point in the same direction and a speeding of response if they point in the opposite direction

(Sumner, Nachev et al. 2007). This effect is the reverse of classical priming effects where congruent stimuli speed reactions and is known as the negative compatibility effect (NCE). The NCE is thought to be generated as a result of automatic inhibition of response plans that are not subsequently carried out. Presumably this function is critical for allowing information in favour of one response plan to accumulate and pass the threshold for action execution (Cisek and Kalaska 2002; Cisek and Kalaska 2005; Cisek 2007).

Masked primes have been used to probe motoric, rather than visual processing. Evidence that motor systems are selectively activated by such primes comes from experiments where different primes are associated with movements of the right or left hand or the foot (Eimer, Schubo et al. 2002). A prime that specifies a response using the hand does not modulate reaction times when the target indicates the foot should be moved, although the hand prime does interfere with subsequent target-activated hand movements. Despite the shared directional association of left foot and left hand (and right foot and right hand) primes, there is no cross-over between effectors. Further, a small lesion in the supplementary eye field has been shown to reverse masked priming of eye, but not hand, movements, whereas a large lesion of the supplementary motor areas reverses automatic inhibition of both eye and hand movements (Sumner, Nachev et al. 2007). Therefore, inhibition of the primes appears to occur in an effector-specific manner, most likely at the motor output stage of processing.

In this chapter we use a masked prime task where all stimuli are presented in the vertical midline and responses are required using a centrally placed joystick.

The aim of the study was to investigate whether parietal damage impairs processing of leftward action plans, engendered by the prime, and secondly whether automatic inhibition is intact in these patients with right hemisphere stroke with and without neglect.

4.2 Methods

4.2.1 *Participants*

17 patients with right hemisphere stroke (12 neglect - **Table 1**)) and 12 age-matched healthy controls (7 female, all right-handed, average age 63.5 years) were recruited.

Table 4.1 Clinical information for all patients

Age (years)	Time since stroke (months)	Bells R-L cancellation score	Line bisection (mm to the right)	All 3 SOAs Y/N
Neglect				
77	6	3	-2	Y
46	2	3	6	N
76	99	4	8	Y
67	4	8	12	Y
66*	0.4	1	5	Y
61	1	8	9	Y
41	2	4	8	Y
68	2	12	10	N
45	1	7	10	N
39	2	10	18	N
63*	1	3	1	Y
Median 62	**2**	**4**	**8**	
Non-neglect				
68	7	0	-2	N
66*	1	0	1	Y
42	0.5	-2	0	Y
57	2	2	4	N
67	3	2	4	N
56	48	2	4	Y
Median 61.5	**2.5**	**1**	**2.5**	

* blue text indicates significant reversal of the NCE

4.2.2 *Apparatus and experimental paradigm*

Patients were positioned approximately 100cm from a 15" Sony Vaio (PCG-5A1M) laptop screen where stimuli were presented centrally using Presentation (Albany, USA) software (**Fig 4.1**).

Initially subjects fixated a central box that disappeared 200 ms prior to prime onset (**Fig 4.1**). The prime was presented for 32 ms (2 screen refreshes) and followed immediately by a mask consisting of 30 randomly oriented lines that was presented for 100ms. Then a blank screen was shown for 100ms before a target arrow was presented for another 100ms (i.e. SOA =200ms). Subjects were required to respond as fast as possible to the target arrow using a centrally placed joystick and were instructed to keep their gaze on the laptop display. With an SOA of 200ms, many previous experiments have shown that there is a reaction time *cost*, negative compatibility effect, when the prime and target point in the same direction compared with when they point in opposite directions or the prime is neutral (no directional association) (Sumner 2008).

Masking rendered the prime imperceptible. To ensure the prime had been successfully masked, all subjects were asked to describe what they saw after the first block and, at the end of the experiment, subjects were asked if they saw any arrows other than the ones following the hashed lines, and none did. Inter-trial interval was 2s after initiation of the response. Eye position was monitored by the experimenter. A short practice session (< 2mins) took place before the start of the first block.

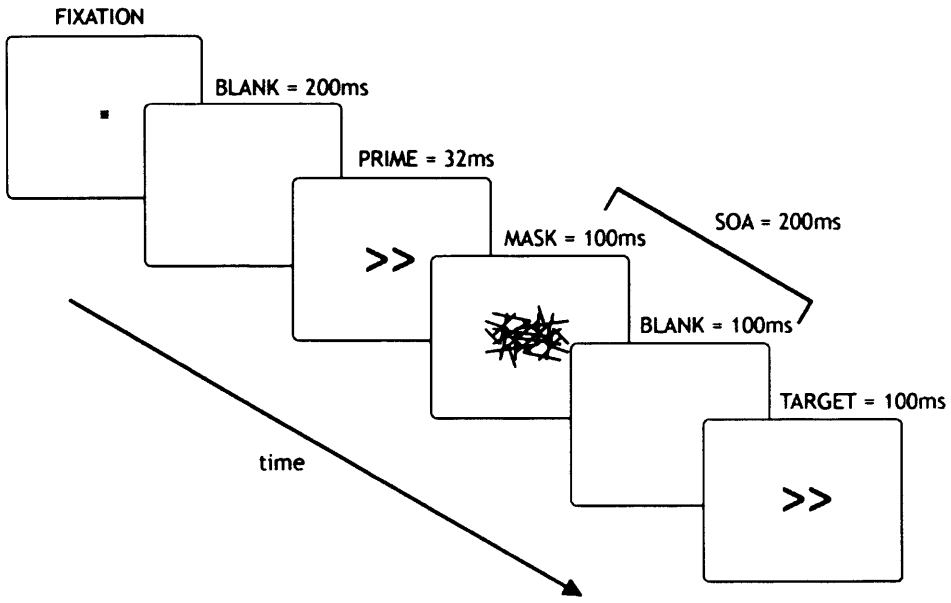


Figure 4.1 Masked prime paradigm
Subjects respond using a centrally placed joystick to the target arrow. This arrow is preceded by a prime that is not visually perceived as it is masked. The SOA (stimulus onset asynchrony) is 200ms (times between onset of mask and onset of target).

Arrow stimuli were designed so that the directional information would be available to patients even if they had a hemianopia or 'object-based' neglect; each arrow comprised two chevrons pointing in the same direction and subtended approximately 1.5 x 1 degrees visual angle. Neutral primes comprised the arrows rearranged so that they carried no directional information; they formed a square (not shown) and covered the same area as the arrow stimuli.

There were 12 blocks of 24 stimuli and stimulus presentation was randomized with the constraint that each condition occurred the same number of times per block. There were six different trial types (**Table 4.2**).

Table 4.2 Trial types

Prime	Target	Trial type
Left	Left	Left congruent
Right	Left	Left incongruent
Neutral	Left	Left neutral
Left	Right	Right incongruent
Right	Right	Right congruent
Neutral	Right	Right neutral

4.2.3 *Data analysis*

Repeated measures ANOVA was performed on raw median RT data for each subject group separately and also jointly with subject group as a between subjects factors and direction and prime type as within subjects factors. Post hoc pairwise comparisons were performed with bonferroni correction where appropriate.

Previous work has suggested elderly people who respond slowly have a reduced NCE (Schlaghecken and Maylor 2005). Therefore to control for differences in reaction time and possible generalised failure to process masked primes, subsequent data are considered firstly as a proportion of the neutral reaction time for each individual and secondly only lateralised differences (in prime direction) are considered in the next analysis. Since we are suggesting

that failure to process competing leftward prime is a lesion-specific rather than neglect-specific disorder, the right hemisphere patients, neglect and non-neglect, are considered together except where stated.

The hypothesis was that patients with PPC damage would propagate leftward directional programs less well than rightward. Therefore the magnitude of the effect of the left prime compared to the right prime was the subject of the next investigation. The magnitude effect of the left prime was calculated as:

$$((|LC-LN|)/LN)+((|RN-RI|)/RN)$$

and the effects of the right prime:

$$((|RC-RN|)/RN)+((|LN-LI|)/LN)$$

where RC = median right congruent RT, RI = median right incongruent reaction time, RN=median right neutral reaction time, LC = median left congruent RT, LI = median left incongruent reaction time and RN=median left neutral reaction time.

The magnitudes of the left and right prime effects were compared in normal subjects and the right hemisphere stroke groups using Wilcoxon signed rank test as data were non-parametrically distributed. Correlations were sought between reduced magnitude of left prime effects and neglect severity using spearman's non-parametric correlations and left prime effects in right hemisphere patients with and without neglect were compared using the Mann Whitney test.

Next possible impairments of non-lateralised inhibitory processes, automatic inhibition leading to the NCE, were investigated. Some patients, who may be old or slow, are expected to have little impact of the prime at SOA 200ms (Schlaghecken and Maylor 2005). Therefore specific interest lies in any patients who might show significant within subject reversal of the expected NCE. Incongruent and congruent RTs were compared using an independent sample T-test of each patient's data.

4.2.4 *Lesion mapping*

All patients' lesions were plotted using MRICro software (available at www.mricro.com) from routine clinical imaging, either CT or MR, on the CH2 template to create an ROI (region of interest) on the axial images at Z coordinates: 56, 61, 66, 69, 75, 85, 88, 92, 96, 102, 108, 120. Brunner-Munzel rank order test (NPM for windows www.sph.sc.edu/comd/rorden/mricron/) was used to establish which areas were associated with relatively reduced magnitude of left prime effects (Magnitude of left – magnitude of right prime effects). The statistic was calculated only at regions where at least 3 or more subjects were affected and bonferroni correction was applied (post-correction significance level of $p<0.05$). Lesion volume was calculated for each patient using MIPAV software (version 4.0.1, NIH, Bethesda, Maryland) and correlation was sought between lesion volume and relative impairment of left prime processing using spearman's rho as lesion volume data were not normally distributed.

4.3 Results

As expected normal subjects were slower to move leftward or rightward when a congruent prime preceded a target i.e. they demonstrated a NCE at SOA 200ms (**Fig 4.2**). Repeated measures ANOVA on the raw median RT data revealed a main effect of prime type ($F(2,22)=14.909$, $p<0.005$) and no interactions. Post hoc pairwise comparisons showed significant differences between congruent and both neutral and incongruent RTs ($P<0.05$ after Bonferroni correction), but no differences between neutral and incongruent RTs.

Neither neglect nor non-neglect patients displayed a NCE. In addition, there was variability within these groups (**Fig 4.2**). Repeated measures ANOVA on the raw RT data revealed no main effect of prime type in the patient groups and when compared to the normal controls, there was an interaction of prime type and subject group ($F(4,52)=3.167$, $p<0.05$). Post hoc testing showed that this resulted from a NCE in normal subjects, but none consistently in stroke controls. There was a significant between subjects difference in raw RT ($F(2,26)=4.47$, $P<0.05$) with post hoc tests showing that the neglect patients were generally slower than either of the other two groups. Figure 4.2 suggests a trend toward neglect subjects moving more slowly for leftward than rightward movements, but ANOVA on the RT data shows that this is only a general trend that does not reach significance and there is no significant interaction with prime type ($p>0.1$). The prediction is that stroke patient performance will depend critically upon lesion location. Thus variability within the group was

expected. In the following analyses, specific hypotheses generated following the conflict chapter are investigated.

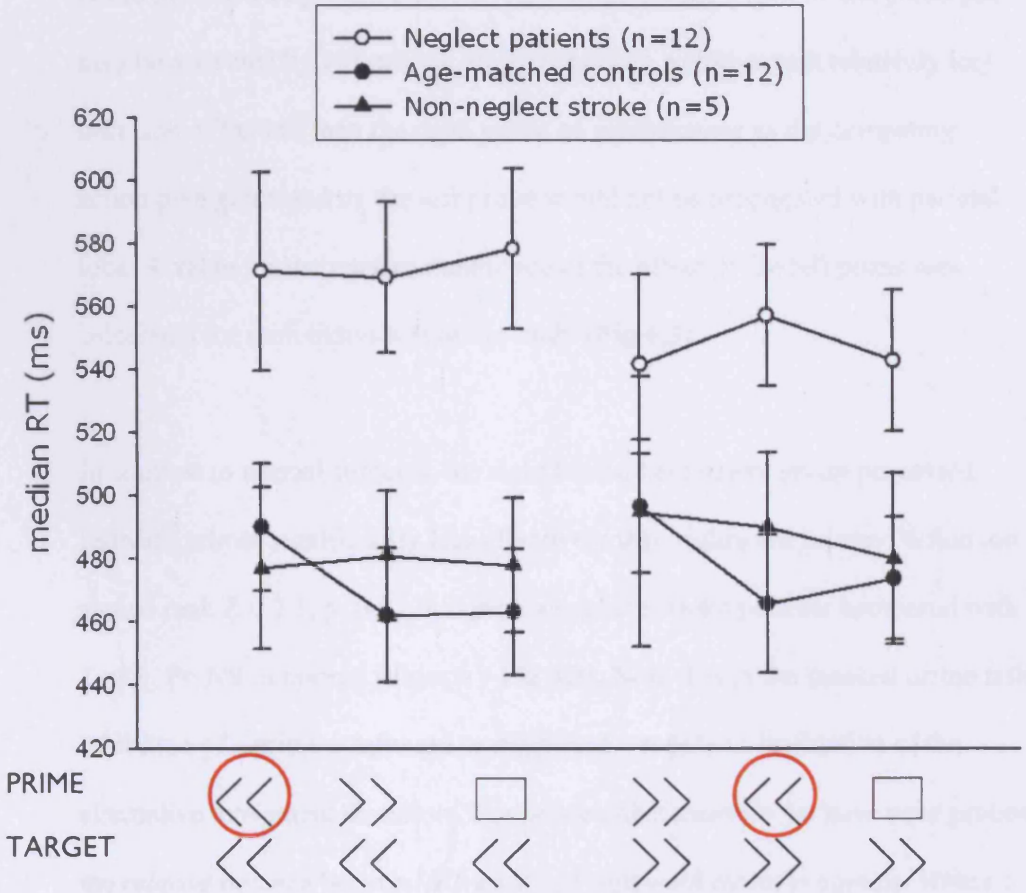


Figure 4.2 Median RTs
Age-matched healthy controls are slower when primes are congruent than when they are incongruent or neutral. This pattern does not occur in stroke patients with or without neglect. Conditions in which there is a left prime are circled.
Note that the trend toward neglect patients responding more slowly for left than rightward movements across all three conditions (neutral, congruent and incongruent) is not significant.

4.3.1 *Magnitude of the effect of the left primes reduced in patients with PPC damage*

Conflict data presented in chapter 3 suggested that patients with PPC damage fail to process competing leftward response programs which in this paradigm may be activated by left primes. In that case one would expect relatively less intrusion of the left than the right prime on performance as the competing action plan generated by the left prime would not be propagated with parietal lobe. A value for the relative magnitude of the effect of the left prime was calculated for each individual in the study (**Fig 4.3**).

In contrast to normal subjects, the right hemisphere stroke group processed leftward primes significantly less effectively than rightward primes (Wilcoxon signed rank $Z = 2.1$, $p<0.05$ in right hemisphere stroke patients compared with $Z=1.3$, P= NS in normal subjects - **Fig 4.3**). Note that in the masked prime task, **inhibition of a prime – leftward or rightward – results in facilitation of the** alternative movement direction. The prime effect measure we have used probes the *relative balance* between leftward and rightward motor programs. Hence it is the within individual difference between left and right prime effects rather than the absolute magnitude of prime effects that is important. Thus we make no claims about absolute differences between control and patient groups, but simply note that the balance between processing left and right primes in the patient group is biased against leftward direction cues.

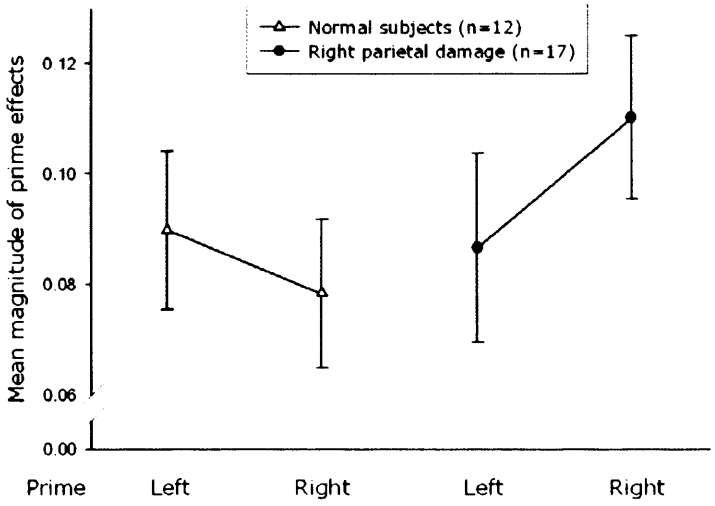


Figure 4.3 Left prime effects: relative magnitudes

In normal subjects, the magnitude effects are similar for both leftward and rightward primes. However, there is a significant difference between leftward and rightward prime effects in patients with right hemisphere stroke such that rightward primes are favoured. These data show the *relative balance* of the effects of directional primes. The relative magnitude of the effect of the left prime is used for subsequent lesion analysis and this is calculated as: left prime effects minus right prime effects.

Within the patient group, there was variability with only some of the patients processing the leftward primes less effectively than right. Therefore we investigated brain regions associated with under representation of the left prime (low value when the magnitude of right prime effects is subtracted from that of left prime effects). Brunner Munzel analysis showed a significant association between damage in the PPC and parietal and occipital white matter and under representation for leftward movement plans following leftward primes (**Fig 4.4**). There was no correlation between the magnitude of left prime representation and lesion volume (Spearman's rho = -0.047, NS) and neither

the presence nor the severity of neglect correlated with this measure (Pearson correlation = 0.23, NS).

We also asked if reduction in the left prime magnitude could be associated with the presence of neglect. Spearman non-parametric correlation did not suggest a correlation between neglect severity and reduced processing of the left prime (Spearmans rho = 0.261, NS). Further, direct comparison of neglect and non-neglect patients showed no different in the relative leftward prime effects between the groups (Mann Whitney U Z= -0.949, p=0.383). Thus the effect is lesion-specific rather than neglect-specific.

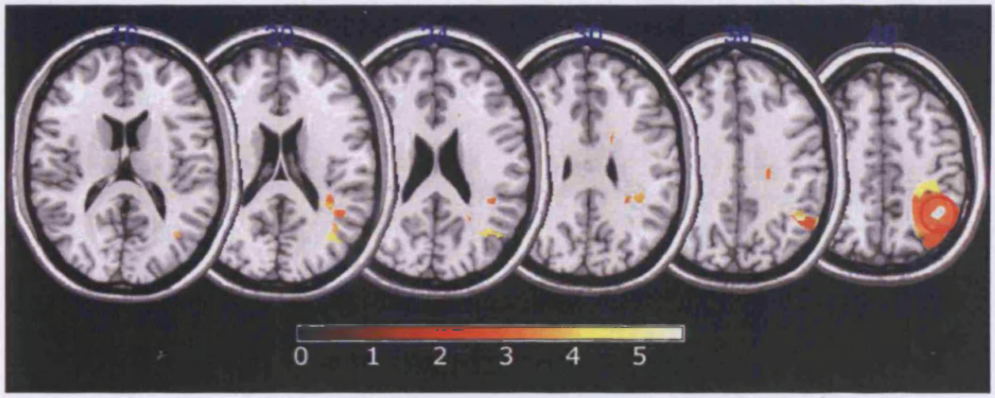


Figure 4.4 PPC associated with relatively poor activation of leftward compared to rightward motor programs.

Damage in the areas (highlighted by the red circle) is in the white matter underlying the angular gyrus and the supramarginal gyral white and grey matter. This region is significantly associated with diminished processing of leftward, but not rightward primes. The coordinates for the most significantly affected area is x= 34, y= -52, z= 40 with Z scores 5.77 respectively. Z scores above 4.72 are significant after Bonferroni correction ($p<0.05$).

4.3.2 *Reversal of NCE in 3 patients*

So far, the lateralised directional differences within patients have been considered. However, unlike normal controls, patients as a group did not show a NCE in this task in either direction. Is this just because the effect of the primes in general is reduced due to the age and relatively slow responding of the stroke subjects (Schlaghecken and Maylor 2005), or are there patients within this group who have a significant within-subject reversal of the NCE? In order to establish this, those patients with significant within subject reversal of the NCE were sought.

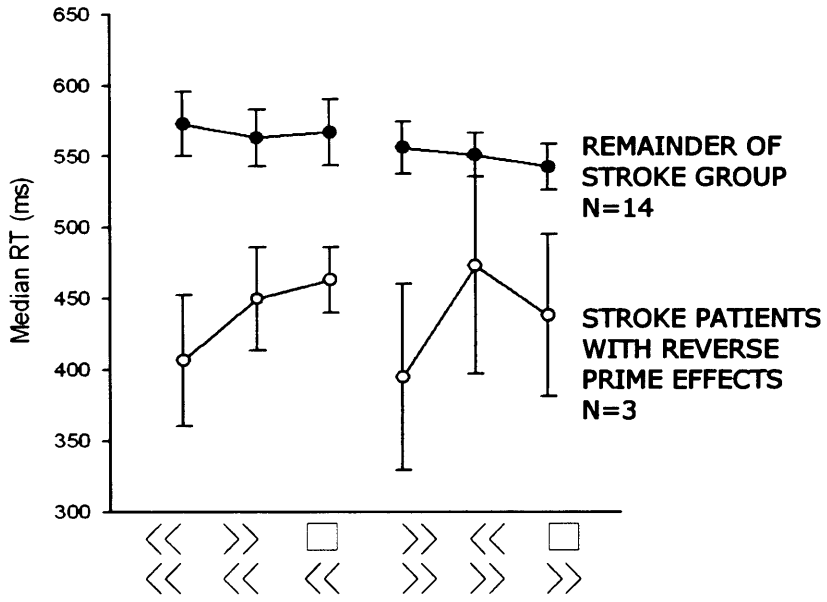


Figure 4.5 Three patients with significant reversal of NCE
Reversal was assessed by comparing incongruent and congruent reaction times within each individual. Only 3 patients showed significant reversal.

Independent sample t-test on each individual's RT data revealed significant slowing in the incongruent compared to the congruent condition in three stroke patients (blue text in **Table 4.1, Fig 4.5**). Two of these patients had neglect and the third had recovered from neglect by the time of testing. Two of these patients had watershed infarcts including inferior and middle frontal gyri and underlying white matter and one had a discrete thalamic haemorrhage extending into the basal ganglia (**Fig 4.6**). Importantly these patients were not slower than either the rest of the stroke patients or the normal controls. Error rates in one of these patients were extremely high consistent with abnormal intrusion of incongruent information onto performance (**Fig 4.7**). Note that the lesion volume in these patients (5075, 1914 and 1369 voxels = mm^3) was relatively low when compared to the whole group (mean 13589 voxels, SE 3510, range 1369-52346 voxels).

Figure 4.6 Lesion overlay for three patients with significant reversal of NCE

Of the 3 patients with a significantly reversed NCE i.e. who were slower to move in the incongruent than the congruent condition, two had lesions in the inferior and middle frontal white matter and the third had a thalamic haemorrhage that extended slightly into the globus pallidus.

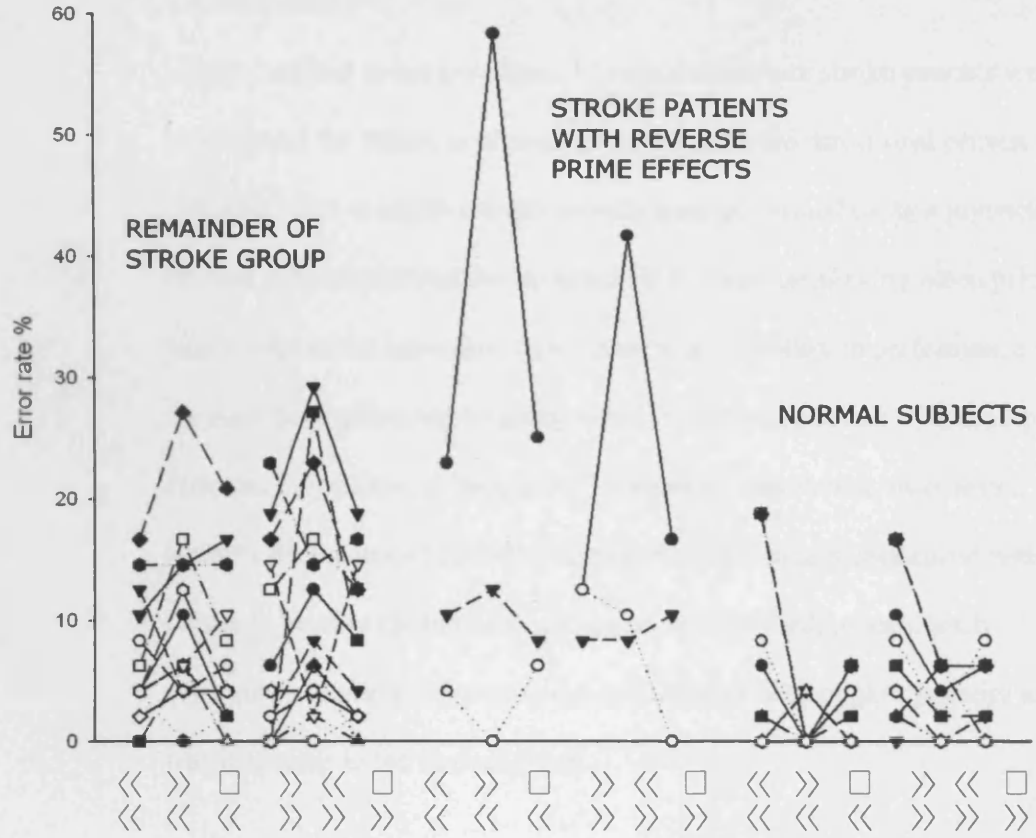


Figure 4.7 Error rates for three patients with significant reversal of NCE compared to other stroke patients and normal subjects

Error rates as well as RTs were markedly higher in the incongruent than congruent or neutral conditions in one patient with frontal damage.

4.4 Discussion

Using a masked prime paradigm, 17 right hemisphere stroke patients were investigated for failure to process irrelevant leftward directional primes when either leftward or rightward movements were performed using a joystick. Normal subjects showed the expected NCE, response *slowing* when prime and target point in the *same* direction. There was variability in performance within the right hemisphere stroke group which comprised patients with multiple different lesion sites, including PPC. Brunner Munzel rank order lesion analysis demonstrated that PPC damage was specifically associated with failure to process the leftward, compared to rightward, primes. Such asymmetry of prime processing did not correlate with neglect severity and nor was it specific to the neglect group.

Further analysis on this data revealed three patients in whom the NCE was completely reversed (for both left and right primes and direction of movement). Therefore variability within the neglect group was contributed to by at least two factors: relative failure to process leftward primes and generalised reversal of priming effects. As discussed above, the first abnormality was commoner in patients with PPC lesions, implicating this region in processing leftward competing response programs. In contrast, patients with a reversal of the NCE all had more anterior damage either in the frontal white matter or thalamus and basal ganglia.

Relatively diminished processing of unconscious leftward response plans did not correlate with neglect severity and nor was it specific to the neglect group

of patients. Therefore there is no evidence from this study that such failure to process leftward primes is associated with functional impairments. However, it is important to note that several of the patients in the non-neglect group had recovered from neglect. It is possible that while neglect on standard clinical tests is no longer present in these patients, they still manifest some of the component deficits. Failure to process competing leftward motor programs may be one component deficit, present both in patients with and without neglect. Only when such a deficit is accompanied by one or more other component deficits, such as lateralised attentional bias or failure to sustain attention, might neglect be manifest in these patients.

The Brunner Munzel analysis presented here uses a continuous dataset to probe lesion-behaviour correlations in the presence of specific hypotheses. This is unlike conventional statistical techniques where differences are sought between groups pre-selected for a certain clinical syndrome, behaviour or lesion location. The advantage of this technique is that all patients can be included even those with large lesions or those who learn strategies to appear normal on pen and paper tasks, and therefore may not fulfil the criteria for neglect despite a lateralised bias. Also, the Brunner Munzel statistic is a rank order test and is robust when the distribution of data is non-parametric (Rorden, Bonilha et al. 2007).

One possible weakness of this approach is that the behavioural data from the patient group considered as a whole does not necessarily reveal a distinct pattern of abnormality or differ from normal subjects because, for example,

there can be at least two patterns of performance within the patient group. Therefore, the lesion-symptom mapping has to be considered in the context of the specific hypotheses generated in the **Chapter 3**. Specifically, patients with PPC damage were found to have a reversed incongruence cost for rightward movements only, suggesting that competing leftward response programs are normally propagated within parietal lobe. Data presented here are consistent with such a role for the PPC.

Why do three patients have a significant reversal of the NCE? One important thing to note first of all is that this is not likely to reflect a general age or speed-related phenomenon. These patients were not particularly slow when compared either to the patient or normal control groups and neither were they different in terms of age or time since stroke. Lesion volume was lower than the average for the group, so one cannot attribute this reversal to large lesions generally slowing response speed or inhibitory process. All these patients had had or still had neglect, but so did many of the other patients. So this deficit is not neglect-specific.

These three patients all had relatively anterior brain lesions with damage either in frontal white matter or thalamus (**Fig 4.6**). Such lesions may well interrupt the network that is critical for automatic inhibition of prime arrows. Recently, tiny lesions in medial frontal cortex involving the supplementary motor areas have been shown to disrupt automatic inhibition leading to a reversal of the NCE (Sumner, Nachev et al. 2007). Both thalamic and white matter areas damaged in these patients have rich connections to medial frontal cortex

(Nakano, Hasegawa et al. 1993; Schmahmann, Pandya et al. 2007). In context, these data suggest that automatic inhibition of primes involves a network of areas including the thalamus and possibly other prefrontal areas and disruption to this network leads to failure of automatic inhibition. One other possible explanation for such a reversal of the NCE, particularly in the patients with inferior white matter damage, is that they have damaged areas that normally filter irrelevant information (Garavan, Ross et al. 1999; Aron, Fletcher et al. 2003). This might perhaps explain the huge error rates for incongruent primes in one of the patients with the reverse NCE.

In the next experiment the time course of the abnormal processing of masked primes is investigated. The aim is to discover whether abnormalities found in experiment 1 represent delaying of the normal response or reduced/reversed processing.

4.5 Experiment 2

Eleven of the stroke subjects, including all three with the reversed NCE, went on to perform the masked prime paradigm at SOAs of 100 and 300ms along with 9 and 11 normal controls respectively (**Table 4.1**). The rationale for using these further two SOAs was to investigate the time course of abnormalities found earlier. In experiment 1, patients with relative failure to process the left prime were shown to have damage in PPC. If such lesions *delayed* processing the left prime, but the eventual amplitude of the left prime-induced action was normal, we expected that the relative magnitude of the effect of the left prime for the patients would be larger at SOA 300ms than at SOA 200. In other words, the effect of the left prime would start to kick in later, around 300ms perhaps, whereas the effect of the right prime would already be declining. However, if the left prime processing is truly diminished rather than just delayed one would expect the magnitude value to be the same or less at SOA 300ms than 200ms.

4.6 Methods

The paradigm was similar to that above except that in one session the SOA was 100 ms and in a second session the SOA was 300ms. The order of the sessions was counterbalanced across individuals and sessions were all at least 1 day apart.

Again the magnitude score was calculated for each individual at each SOA. In addition, for the 3 patients who had significantly reversed NCEs in experiment 1, the non-lateralised effect of the primes at the three SOAs was calculated.

4.7 Results

Normal subjects did not have a significant NCE at either of these two SOAs (**Fig 4.8**). Overall in the patient group, the effect of the left prime did not significantly differ between SOAs (**Fig 4.9**). Of the 11 patients who performed both the 200 and 300 ms task, six had a slightly increased effect of the left prime between 200 and 300 ms (3 with PPC damage) and five had a reduction (3 with PPC damage). Therefore there is no evidence of a systematic increase in the effects of the left prime between SOA 200 and 300 in patients with right hemisphere stroke as would be expected if the processing of the left prime were just delayed compared with the right.

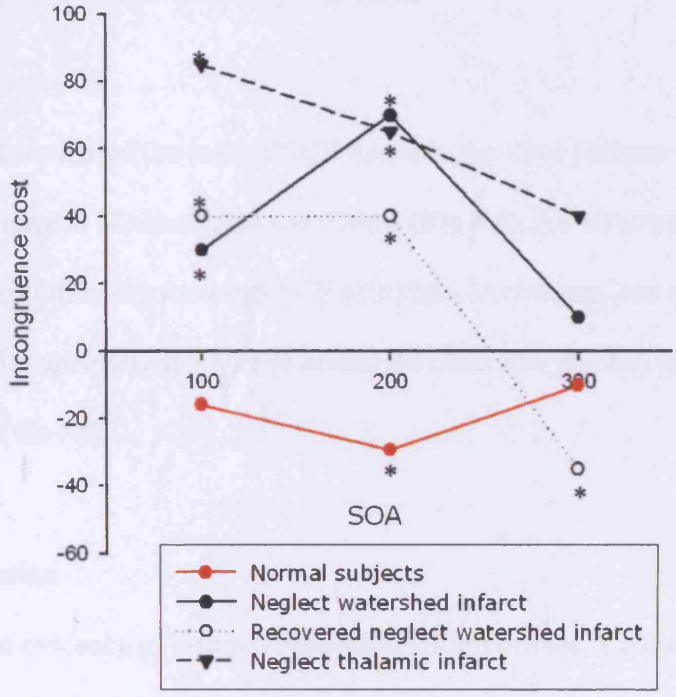


Figure 4.8 Incongruence costs at 3 SOAs
Normal subjects had a significant NCE at SOA 200ms only. All patients who had a significantly reversed NCE at 200ms also had the reversed effect at 100ms SOA. One of the three then developed a significant NCE at 300ms. The other two still had a non-significant reversal of the NCE at 300ms. * indicates significant effect

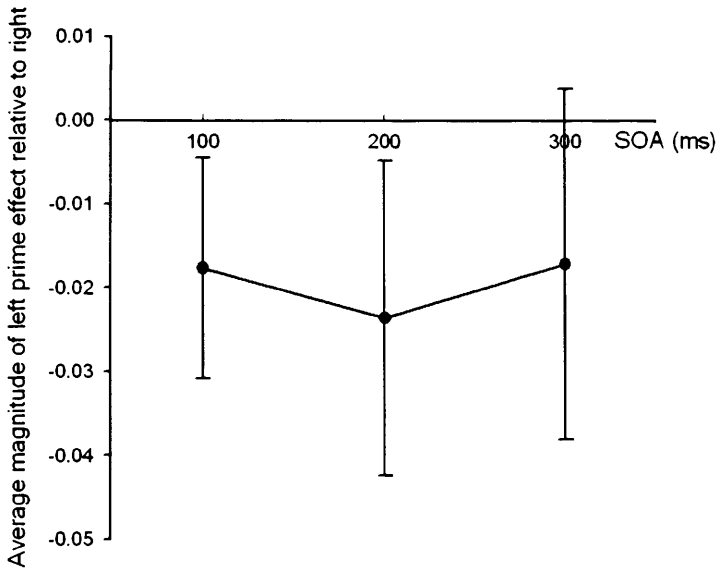


Figure 4.9 Relative effect of left primes compared to right across three SOAs The effect of the left prime did not significantly differ across all 3 SOAs. Error bars represent standard error of group mean.

Next we investigated the loss of NCE found in the three patients with inferior frontal damage at SOAs of 100 and 300ms (**Fig 4.8**). All three patients also showed a significantly reversed NCE at 100ms. In contrast, one of the patients had a significant NCE at 300ms whereas the other two just had non-significant reversal of the NCE.

4.8 Discussion

There is no evidence of delayed processing of left primes in patients with neglect. Therefore, it appears perhaps likely that in patients with right hemisphere stroke, the effect of the left prime is relatively reduced rather than just delayed.

In contrast, there was evidence in at least one of the patients with a watershed infarct, affecting predominantly the anterior white matter, of delay in NCE rather than pure reversal. This patient had significantly reversed NCE at SOAs of 100 and 200 ms but developed a significant NCE at SOA 300ms.

4.9 General discussion

Sixteen patients with right hemisphere stroke and twelve age-matched controls were tested on a masked prime paradigm in which prime arrows were never visually perceived, but did influence subsequent reaction times to a target arrow in normal subjects, such that congruent prime-target pairs resulted in reaction time slowing (Eimer and Schlaghecken 1998; Eimer 1999; Sumner, Nachev et al. 2007). Lesion-symptom correlation within the stroke group suggested that prime-activated competing leftward motor plans are processed less effectively than rightward in patients with right PPC damage. Investigation of the time course of this effect using 3 SOAs indicated that there is likely to be relative reduction rather than delay in processing leftward plans. In addition we found three patients out of a group of seventeen who showed the reverse effect of primes from that in normal controls i.e. congruent primes speeded and incongruent primes slowed responses to the target. One of these patients subsequently developed normal interference of the primes at SOA 300ms suggesting perhaps that automatic inhibition in this patient was delayed rather than absent.

Patients with right PPC damage fail to process leftward compared with rightward competing prime-induced motor plans, at least relative to other

patients. In other words, left primes influenced performance relatively less than right primes in patients with PPC damage. Calculation of the magnitude left vs right prime effects controlled for movement direction; left prime effects for both leftward and rightward movements were considered and likewise for the right prime (see **Methods**). So this measure is a true reflection of how *competing* motor programs, engendered by the primes, are processed. Using such a measure was important to discover how motor programs that are never acted upon, and therefore must be inhibited, are processed in patients with stroke.

Our findings here, that patients with PPC damage selectively fail to process leftward prime-induced competing motor programs, is consistent with that found in chapter 3 when leftward flankers (visually perceived) induced the competing motor plans (Botvinick, Nystrom et al. 1999; Casey, Thomas et al. 2000; Botvinick, Cohen et al. 2004). Only patients with PPC damage and neglect actually had facilitation in the right incongruent condition, suggesting perhaps that failure to process leftward flanker-induced competing motor programs was neglect-specific. In this chapter, the patient with the largest asymmetry favouring right over left prime-induced response plans did not have neglect. Thus this deficit does not appear to be neglect-specific, but rather relates to lesion location, and is perhaps one of many component deficits that when combined lead to manifestation of neglect as measured on standard clinical tasks.

One important question stemming from **Chapter 3** is whether or not the PPC is truly implicated in motor, rather than sensory, processing. In other words, could the failure to process left primes be due to the abnormal representation or decoding of leftward sensory information or is it really generation of the competing leftward motor plan that is lost when the PPC is damaged?

Most observers consider that masked primes activate motor plans that are subsequently inhibited (Eimer, Schubo et al. 2002; Sumner 2008). However, there is some data that suggest the NCE seen in masked prime paradigms may be due to mask-induced activation of stimulus response associations opposite from the prime stimulus. Thus it would not be the prime that is automatically inhibited, but the opposite stimulus response association, activated by the mask, that inhibits subsequent target stimuli pointing in the same direction as the prime. Modulation of mask features (removing components opposite to the prime) reveals that mask-induced activations cannot explain the whole of the NCE, but they do contribute to the effect (Sumner 2008). Therefore, it is possible that patients with PPC damage fail to generate the second, mask-induced response plan following a left prime perhaps because of abnormalities in sensory encoding. Although unlikely that such a primary perceptual deficit would produce directionally lateralised findings, it is hard to exclude absolutely using our data.

Even if one assumes that it is the prime and not the mask that is processed abnormally in patients with PPC neglect, there is still the possibility that such patients fail to decode the leftward prime stimulus i.e. even though they are not

expected to 'see' the prime, it still has to be decoded or given it's leftward meaning. Such a signal-response decoding role for the PPC has been suggested by previous functional MRI work (Bunge, Hazeltine et al. 2002; Cavina-Pratesi, Valyear et al. 2006). Since there was no significant difference between leftward and rightward response times overall in the patient group, there appears to be no problem decoding target leftward stimuli, but the possibility remains that patients with PPC fail to decode leftward prime arrows. Distinguishing a true motor from a stimulus response decoding role can only be achieved perhaps if PPC patients fail to generate competing leftward response plans in the absence of directional visual stimuli. This is further investigated in Chapter 5.

Three patients in our study did show significant non-lateralised reversal of the NCE at SOAs of 100 and 200ms. This effect has been described once before, but those patients had damage to the supplementary motor area and supplementary eye fields (Sumner, Nachev et al. 2007). In that study, the response required was either a right or left button press or rightward or leftward eye movements and the reversal occurred only for eye movements in the patient with SEF damage and for both eye and hand movements in the patients with a slightly larger SMA lesion. In the data described above, directional movements were required using only the right hand. The different loci of injury in the patients described here could reflect damage to an effector-specific region concerned with directional arm movements. However, since there was no area of overlap between all 3 patients, this seems unlikely.

Instead, it is possible that the regions damaged in these patients are normally connected to the SMA forming a network. This is a plausible explanation as one lesion involves the thalamus that is well connected to the medial frontal cortex (Nakano, Hasegawa et al. 1993) and the other two patients have damage within frontal white matter that could be relaying information to or from the SMA. Another possible account of these data is that there is damage to regions that normally filter irrelevant information. In two of the patients the inferior frontal white matter is infarcted and this could lead to increased intrusion and delay following incongruent primes reversing the NCE (Garavan, Ross et al. 1999; Aron, Fletcher et al. 2003). Such intrusion of irrelevant information may result in an increase in RT in the incongruent condition, thus overwhelming the effects of automatic inhibition (overall RT would be a composite effect of the two systems). This could explain the huge error rate found in one of these patients when primes were incongruent.

Finally, it is interesting that one of the patients with a reversed NCE at SOA 200ms actually developed a significant NCE at SOA 300ms. This patient could be considered to have inhibitory delay. Normal subjects have classical priming effects (facilitation when the prime and target point in the same direction) when there is a very small separation between the prime and the target (0-50ms SOA) (Eimer 1999). They then develop a NCE (cost when prime and target point in the same direction) at around 100ms which lasts for 100-150 ms before the effect of the prime is diminished. This patient with a watershed infarct on the right side affecting mainly prefrontal white matter displayed a similar pattern of facilitation followed by inhibition, but it was delayed by

approximately 200ms. Such a delay in automatic inhibition in this patient perhaps reflects partial damage to the white matter connecting regions involved in automatic inhibition and consequent slowing of response inhibition.

In summary, although there was great variability within the stroke patient group, it does appear that right PPC processes information necessary to activate leftward directional motor programs. Further, it is possible for patients with intact medial frontal cortex to have reversed NCE suggesting automatic inhibition requires several intact brain regions. In particular, damage to white matter tracts leading to SMA may lead to a slowing of the inhibition whereas perhaps thalamic or inferior frontal lesions abolish inhibitory processes that normally occur following activation of an unwanted motor program.

Chapter 5: Free choice

5.1 Introduction

Several questions are raised by the finding that patients with neglect and PPC damage selectively fail to process competition from leftward information when planning rightward movements (Chapter 3). One important issue is whether or not the deficit observed in individuals with PPC damage is truly motoric or whether it might result from perceptual or attentional factors. There were several internal controls against these accounts within the conflict paradigm used in Chapter 3; since the stimuli and response device were in the vertical midline and the abnormal finding was for one direction only, spatial and attentional explanations for the abnormal conflict processing were unlikely.

Previous functional imaging studies have provided evidence that the parietal lobe has a role in *decoding* stimulus-response relationships (Bunge, Hazeltine et al. 2002; Cavina-Pratesi, Valyear et al. 2006). This possibility was also considered as an explanation for the result in Chapter 3, but the patients were able to interpret leftward target (central) arrows, making a general failure to process stimuli with a leftward response association also unlikely. Nevertheless, it still remains a possibility that PPC damage impairs stimulus-response processing of *competing* leftward arrows only, i.e. leftward signals are decoded normally when they are dominant (in the target location), but not encoded normally when they are flanking (in a peripheral, competing location).

In the next experiments, the possibility that failure to represent competing leftward motor plans observed in right-hemisphere neglect patients is truly a

motor deficit is investigated. In addition, the potential relevance of lateralised competitive bias to the manifestation of neglect is explored since it remains unclear whether the deficit in processing leftward competing cues is related to neglect severity.

Both paradigms used in this chapter require patients with PPC damage to make a 'free' choice between two possible alternatives. Subjects are forced to make a choice, but crucially there is no visual information to guide their decision. In this 'underdetermined' response situation, the two motor plans – leftward and rightward – are considered to be maximally in conflict because there are only two alternatives and neither is favoured by any external factors, such as visual cues (Botvinick, Braver et al. 2001; Nachev, Rees et al. 2005).

Much emphasis has been placed on the difference between self-generated or underdetermined actions, such as those performed in our free choice paradigm, and instructed movements, where the stimulus environment describes only one possible action choice (Frith, Friston et al. 1991; Lau, Rogers et al. 2004; Nachev, Rees et al. 2005; Waszak, Wascher et al. 2005; Lau, Rogers et al. 2006; Procyk and Goldman-Rakic 2006; de Jong and Paans 2007; Milea, Lobel et al. 2007; Mueller, Brass et al. 2007; Nachev, Wydell et al. 2007; Sumner, Nachev et al. 2007). There are several contrasting interpretations of how different brain regions may interact to generate action under different conditions. It has been proposed that action selection is mediated by inhibition of unwanted action plans in both lateral and medial prefrontal regions (Garavan, Ross et al. 1999; Aron, Fletcher et al. 2003; de Jong and Paans 2007). Lateral

prefrontal cortex has been found to inhibit action in general (stop movements) whereas medial prefrontal selectively inhibits certain actions (facilitates movement selection) (Garavan, Ross et al. 1999; Aron, Fletcher et al. 2003; de Jong and Paans 2007).

Some authors argue for functionally and anatomically distinct networks for internally and externally generated action with frontostriatal circuits mediating internally-selected action, whereas externally-guided action requires lateral premotor and parietal areas (Waszak, Wascher et al. 2005; Keller, Wascher et al. 2006; Brass and Haggard 2007). However, an alternative view is that all motor programming is built on automatic activation of action plans in response to a combination of environmental stimuli and contextual knowledge based on memory of past experience and ongoing goals (Sumner, Nachev et al. 2007). So rather than there being absolute differences between self-generated and externally driven action, differences lie only in the degree to which stimulus driven 'external' or goal-driven 'internal' processing streams are recruited (Jahanshahi, Jenkins et al. 1995).

When action is relatively 'underdetermined' or internally generated, most authors consider that medial frontal regions are involved in movement selection. There has been debate as to whether the cingulate (Mueller, Brass et al. 2007) or pre-SMA (Lau, Rogers et al. 2004; Lau, Rogers et al. 2006) is the critical area for such 'internally generated' movement. This discrepancy probably reflects the different requirements of each paradigm. In functional imaging studies, parietal areas are also active when subjects are required to

make internally generated actions (Jahanshahi, Jenkins et al. 1995; Lau, Rogers et al. 2004; Elsinger, Harrington et al. 2006; Mueller, Brass et al. 2007; Ogawa and Inui 2007) with one study showing parietal activation to be correlated with the number of possible response choices (Lau, Rogers et al. 2004).

In the experiments described below, underdetermined responding is used as a tool to investigate movement choice bias in patients with PPC damage and neglect. In the first experiment, we devised a choice task, in which on half the trials subjects were asked to freely select between making leftward or rightward movements as quickly as possible; whereas on the other 50% of trials they were *instructed* which way to move **(Fig. 5.1)**.

The stimulus to freely choose left or right comprised two squares which carried no directional information (the neutral cue in the conflict paradigm used in chapter 3). Therefore, there are neither rightward nor leftward *visual* cues in this condition. Importantly, subjects respond using a centrally placed joystick and fixate centrally at all times. Therefore perceptual, spatial or attentional factors should not interfere with performance.

We hypothesized that patients with right parietal damage would have a bias toward making rightward movements under such free choice conditions because leftward motor plans would not compete equally with rightward ones. We also considered that a rightward motor choice bias may be associated with, and perhaps contribute to, more severe neglect.

5.2 Experiment 1

5.2.1 Methods

Sixteen subjects with neglect and 8 without neglect following right hemisphere stroke were tested along with 14 normal controls (**Table 5.1**). Again, subjects moved a centrally placed joystick left or right as quickly as possible. Stimuli similar to those used in the conflict task (Chapter 3), *presented in the vertical midline*, were either congruent arrows all pointing in the same direction (*instructed* condition; 50% of trials) or neutral flankers with no central target (*choice* condition; remaining 50% trials); see **Fig. 5.1**. On choice trials, subjects were instructed to move as fast as possible either left or right. They were explicitly told to move with their first instinct and not to make a plan in advance about their direction of movement. Instructed cues were included to make it harder for subjects to form a plan in advance about which way to go. Stimuli were presented pseudo-randomly with the two constraints that each condition appeared the same number of times per block and that the same stimulus was presented no more than twice in a row. Four blocks of 48 trials were performed giving a total of 196 trials. A short practice session (< 2mins) took place before the start of the first block.

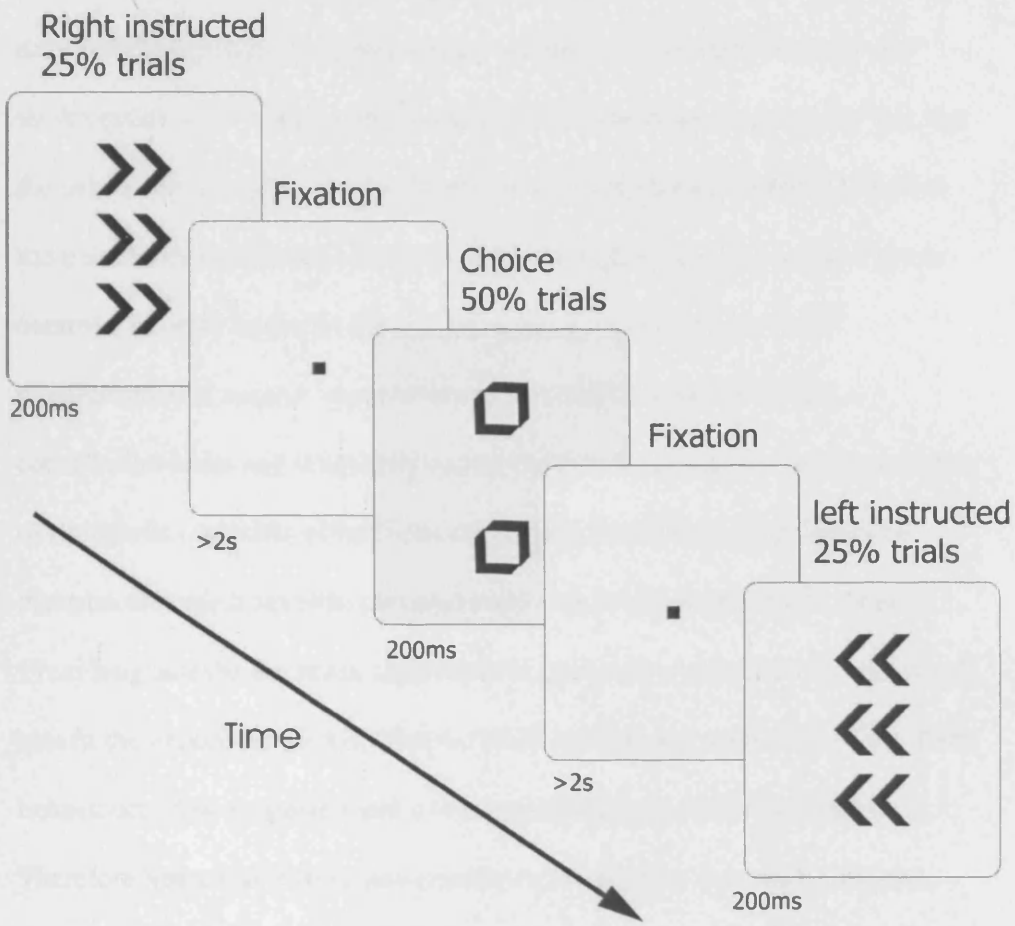


Figure 5.1 Free choice task
Participants had to choose to move either left or right using a joystick as fast as possible on choice trials (50%). In the other 50% of trials, subjects were instructed to move either left or right by arrow cues. Trials were pseudo-randomised with the constraint that the same number of each trial type occurred in each block and that no more than 2 free choice trials in a row were presented.

5.2.1.1 *Behavioural data analysis*

Response choice was analysed using a one-way ANOVA performed on the direction choice data in the free choice conditions for normal controls and stroke patients (with and without neglect). The dependent variable for this was the percentage of rightward movement choices (degree of lateralised bias) in the free choice condition for normal controls, neglect and non-neglect stroke controls. In order to assess the relevance of directional choice to the manifestation of neglect, correlations were sought between the Bell's cancellation score and the percentage of rightward movement choices (number of right bells – number of left bells cancelled). In addition a line bisection measure of neglect severity was also used – each subject bisected 3 lines of 17cm long and the deviation rightward (in mm) was correlated with rightward bias in the experimental task. Shapiro Wilk statistic and inspection of the Bells behavioural data suggested that it was not normally distributed (**Table 5.1**). Therefore Spearman's Rho, non-parametric correlation was used. Only the neglect group was used for this correlation as non-neglect patients by definition would cluster around zero on the Bell's cancellation measure.

Next cumulative binomial probabilities were calculated for each individual (Sheskin 2007). The aim of this statistic is to give the probability that each individual's number of rightward choices would have occurred by chance if they were entirely unbiased on each trial. In other words, if there was actually a 50% chance at each trial of the subject moving right, what is the probability that any individual would move rightward say 57% of the time?

The *cumulative* binomial probability was used as interest lay not in the chance of moving right exactly 57% of the time, but in the probability that the subjects would move right 57% or more of the time. This statistic makes the assumption that each trial in the experiment is completely independent which is perhaps unlikely, but since left or right instructed or chosen movement could precede any choice decision, it is unlikely there was systematic bias by preceding action. Significance testing of the cumulative binomial probability function relies on the fact that the binomial function resembles a normal distribution when sample sizes are large. Therefore for the probability of an event occurring a certain number of times by chance to be statistically insignificant, it must be less than 0.05/2 =0.025, i.e. half the standard value for rejection of the null hypothesis.

Since a response bias in at least some of the neglect patients was anticipated, possible inference from lateralised reaction time data is limited. This is because response bias may confound reaction time variation as rarely made movements would be expected to be slower than frequently made movements. With these considerations, lateralised reaction time data for choice and instructed conditions were analysed together using repeated measured ANOVA with the 3 groups as between subjects variables. Post hoc testing was performed using Bonferroni correction where appropriate. Further, in order to investigate whether a rightward choice bias was associated with generalised leftward movement initiation slowing, a paired t-test was performed comparing leftward and rightward median response times in the instructed condition for each neglect subject who chose to move right more often than left.

5.2.1.2 *Lesion analysis*

Next, the Brunner-Munzel rank order statistic on the continuous behavioural ((number of R- number of L responses) x -1) and lesion data was performed to show areas *selectively affected* in patients with a *rightward bias*. Only areas affected in at least 3 individuals were included in the analysis. Importantly we included all patients with right hemisphere stroke in this analysis (neglect and non-neglect). This was because 4 of the non-neglect group had recovered from neglect and it was a possibility that they still had a rightward bias not detected on standard clinical tasks (**Table 5.1**).

This lesion analysis is post hoc and based on the hypothesis generated in Chapter 3 that a relative rightward bias would be most marked in patients with PPC damage. By way of validation of this technique for exploring lesion symptom correlations, we conducted a subsidiary analysis by dividing the patient group into those with damage in the angular gyrus of the PPC and those without and comparing the rightward response bias of the two groups using an independent samples t-test.

5.2.2 Results

Sixteen neglect patients, 8 non-neglect stroke controls and 14 normal controls performed the task (**Table 5.1**). Overall, neglect patients moved *rightward* slightly more often than leftward (right 53.2% (SE 3.4) vs left 46.8% (SE 4.1) **Fig 5.2a**), but there was considerable variation between individuals, with some showing a bias to make rightward movements and others selecting equally from both directions **(Fig. 5.2b)**.

The first question investigated was whether or not rightward motor choice bias was associated with the neglect syndrome. One-way ANOVA on the percentage of rightward choices for age-matched control, stroke control and neglect patients showed no significant differences between the groups. When cumulative probability scores were calculated for each stroke subject, only one non-neglect and 3 neglect subjects were significantly more likely to move right than left (**Fig 5.3**). So, rightward bias occurs in both neglect and non-neglect subjects – although it might be important to note that the subject without neglect who had a significant rightward bias was one of this group who had recovered from neglect on standard clinical tasks rather than never having had neglect.

We next asked if within the neglect group, rightward bias in movement choice correlated with neglect severity using the lateralised bias on the Bells cancellation as a standard neglect measure (**Fig 5.4**). Spearman's Rho of 0.528, $P<0.05$ suggested a significant relationship between the motoric rightward choice bias and the manifestation of left neglect on this cancellation task. However, this relationship was not found when line bisection rightward deviation was used as a measure of neglect severity. Previous studies have reported dissociation between performance on cancellation vs. line bisection tasks in neglect patients with some authors arguing that cancellation deficits may be better measure of neglect behaviour (Ferber and Karnath 2001).

Table 5.1 Patient information for experiment 1

	Age (years)	Time since stroke (months)	Bells R-L	Line bisection (mm to the right)	Current (neg), recovered or never neglect
	78	1	14	20	neg
	58	35	3	-2	neg
	41	0.06	3	5	neg
	66	0.09	1	6	neg
	41	0.3	13	0	neg
	42	0.2	4	9	neg
	64	0.3	5	8	neg
	36	0.2	0	7	neg
	47	1.5	1	20	neg
	67	1.8	4	22	neg
	66	0.09	10	7	neg
	66	0.25	3	4	neg
	66	0.68	4	10	neg
	46	1.5	14	28	neg
	69	1.13	3	8	neg
	46	0.68	8	18	neg
Median	**61**	**0.5**	**4**	**8**	
	74	0.68	-1	-4	never neg
	31	0.09	0	0	never neg
	24	2.58	0	0	recovered
	63	58.87	0	4	recovered
	70	0.16	0	0	never neg
	53	0.19	1	-2	never neg
	67	0.58	1	3	recovered
	71	2.32	0	4	recovered
Median	**65**	**0.6**	**0**	**0**	

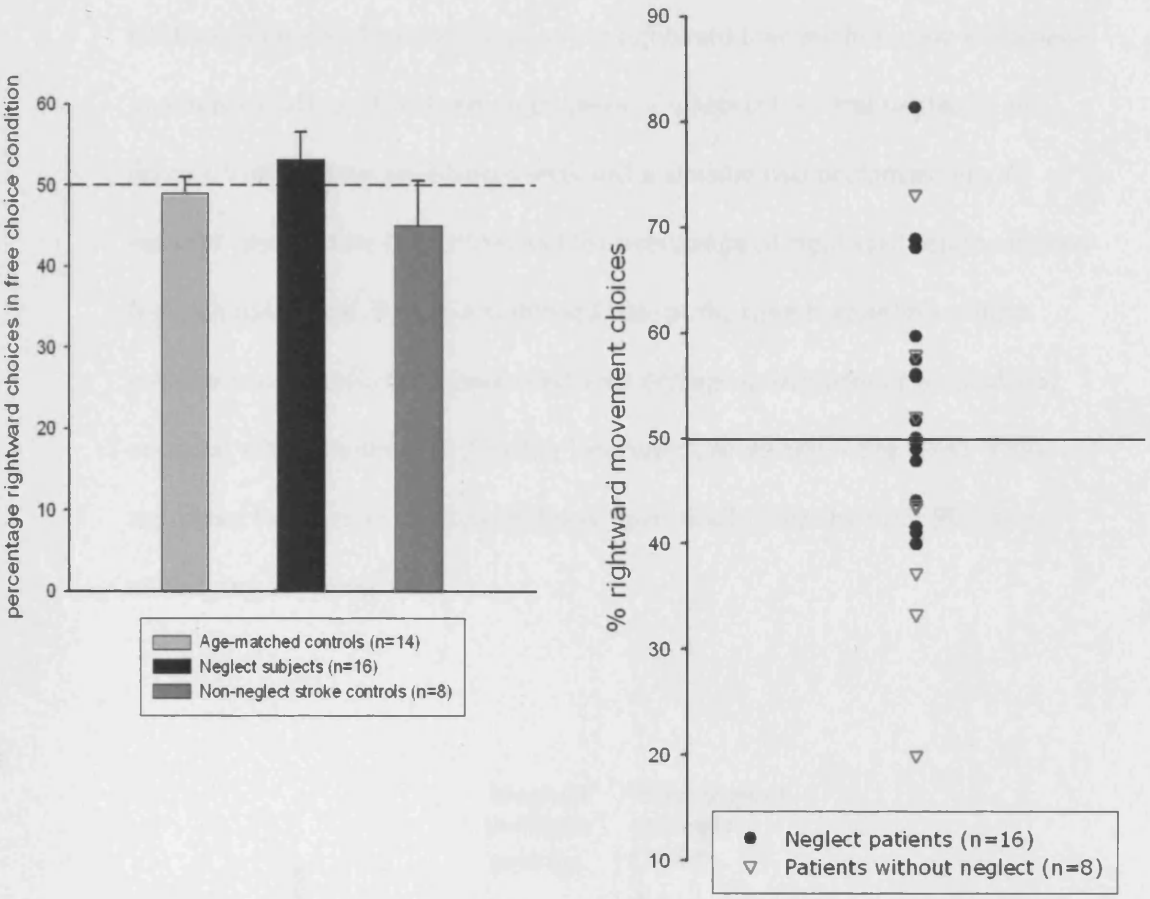


Figure 5.2 Proportion of rightward responses across groups
a) In the choice task, subjects chose to respond left or right on 50% of trials. There were no overall significant differences in group performance.
b) There was variation between subjects with some moving right more often than left (rightward bias) whereas others selected from both movement directions.

Since rightward movement choice bias has been shown in patients with neglect and at least one patient not manifesting neglect on standard clinical tasks, the next question asked was whether or not rightward bias might be due to damage in one particular area of brain, regardless of whether they had neglect at the time of testing. Brunner-Munzel rank order statistic was performed on *all patients' lesion data* (i.e. n=24) and the percentage of rightward action choices for each individual. Relative rightward bias in the right hemisphere stroke patients was significantly associated with damage to the inferior parietal and occipital white matter ($p<0.05$ after Bonferroni correction - **Fig 5.5a**). Thus rightward bias has an anatomical basis, specifically with the right PPC and underlying white matter.

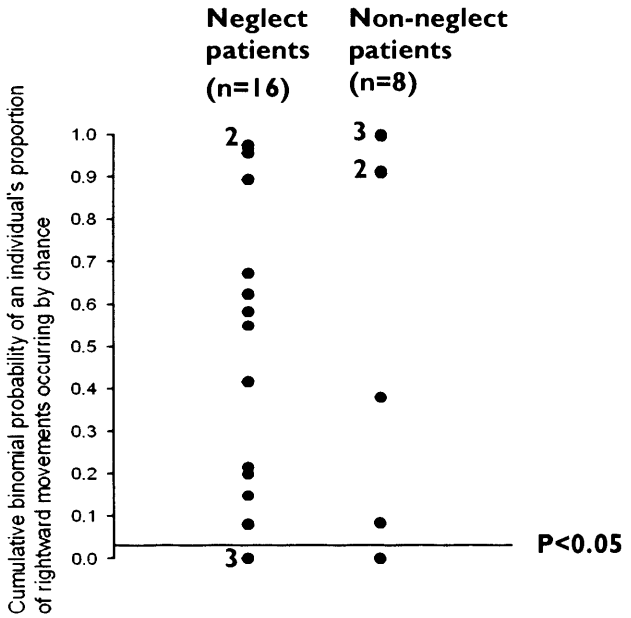


Figure 5.3 Cumulative binomial probabilities for neglect and non-neglect subjects
Using conventional significance testing, only 3 neglect and 1 non-neglect subject would be considered to have a significant rightward bias (indicated by dots below the horizontal axis).

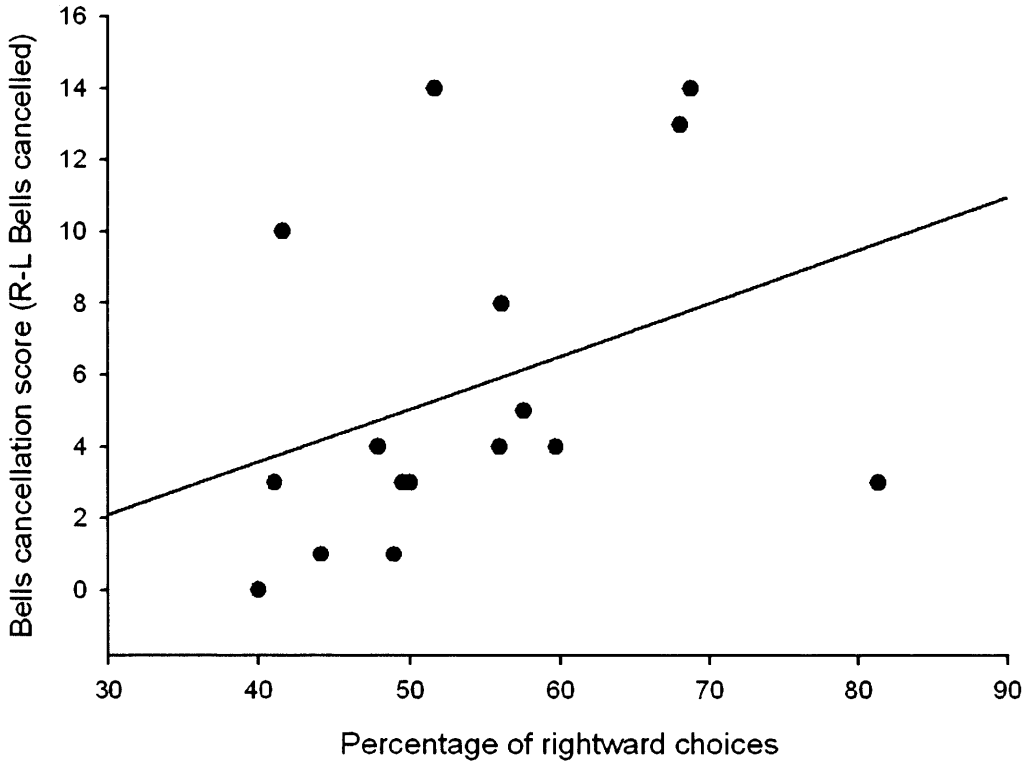


Figure 5.4 Correlation between neglect severity and movement choice bias
Patients who tended to choose to move right in the free choice condition also tended to have the most severe neglect when tested using the Bells cancellation task (Spearman's rho = 0.523, $p<0.05$).

In a subsidiary analysis, patients were divided into two groups, regardless of whether they had neglect, according to whether or not they had damage in the angular gyrus of the PPC (n= 11 with damage in PPC, n=13 without damage in PPC **Fig 5.5b**). There was a significant difference in percentage of rightward responses chosen between those patients with PPC damage and those without ($t = 2.3$, $p<0.05$); PPC patients went right 57 % (SE 2.8) of the time on average compared to 46% (SE 4.0) in the patients without PPC damage. Therefore the post-hoc lesion symptom mapping using the Brunner Munzel statistic (**Fig 5.5a**) and a more conventional technique dividing patients according to their lesion anatomy (**Fig 5.5b**) both implicate PPC as important for resulting in a rightward motoric bias. But the effect need not be neglect-specific

Repeated measures ANOVA on the reaction time data revealed a main affect of instruction type (**Fig 5.6**): all subject groups were slower to move when *choosing* than when instructed to move ($F(1,35)=87.7$, $p<0.001$). In addition there was an interaction between instruction type and subject group ($F(2,35)=8.95$, $p<0.001$). Post hoc ANOVA comparing each group with the normal subjects revealed that this interaction was due to the performance of the neglect patients who differed from the age-matched normal control group ($F(1,28)=17.950$, $p<0.001$), but the stroke control group did not significantly differ from either the neglect or age-matched healthy controls (**Fig 5.6**). So neglect was associated with a choice cost, although this effect was not directional.

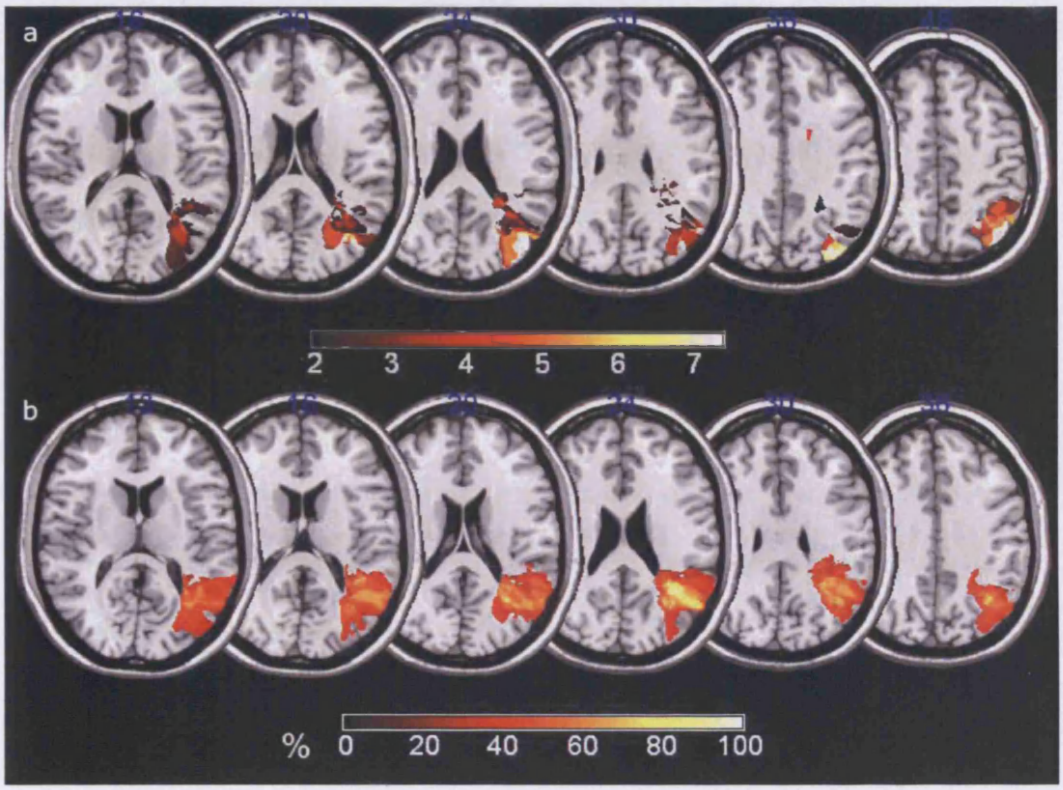


Figure 5.5 Lesion analysis for neglect patients in free choice task
a) Using the Brunner Munzel rank order statistic, cortex of the angular gyrus and surrounding white matter are shown to be significantly associated with a rightward bias, even after Bonferroni correction for multiple comparisons ($p<0.05$). The coordinates of the centre of the significant area on this slice are x=50, y=-64, z=24. A Z score of greater than 4.745 suggests significance after Bonferroni correction.

b) Subtraction showing areas damaged in patients with lesion of the PPC (patients with PPC damage minus those without). Colour bar shows the percentage damaged in PPC group and not in non-PPC group e.g white colour shows that 100% of PPC patients had damage in this area and 0% of non-PPC patients.

Do patients with a rightward choice bias tend to initiate leftward movements more slowly than right even when the movement is instructed? Subgroup analysis of the patients with neglect who chose to move right more often than left showed no significant difference in the reaction times to leftward verses rightward arrows (paired t-test). Median reaction times for the subgroup of neglect patients who moved right more often than left were 695 ms (SE 33) rightward and 660 ms (SE 38) leftward, with 5 patients initiating leftward movements more slowly than rightward and the other 3 moving right more slowly than left. In summary, although right PPC damage was associated with a bias to choose rightward movements more than leftward ones, there was no asymmetry in instructed reaction times.

5.2.3 Discussion for Experiment 1

In this first paradigm, subjects were forced to choose rapidly between rightward and leftward movements with the right hand without any directional visual information being provided. There was variability within the neglect group with a non-significant trend towards these patients making a higher proportion of rightward choices than healthy age-matched controls or right hemisphere stroke controls. Within the neglect group, the tendency to choose to move right rather than left was associated with more severe neglect when measured using the Bells cancellation, a standard clinical test for neglect. When neglect severity was assessed using line bisection, no such relationship to directional response bias was shown. Such dissociations between these two measures, line bisection and cancellation, are well known in neglect patients, with cancellation considered by some to be a more sensitive measure of neglect

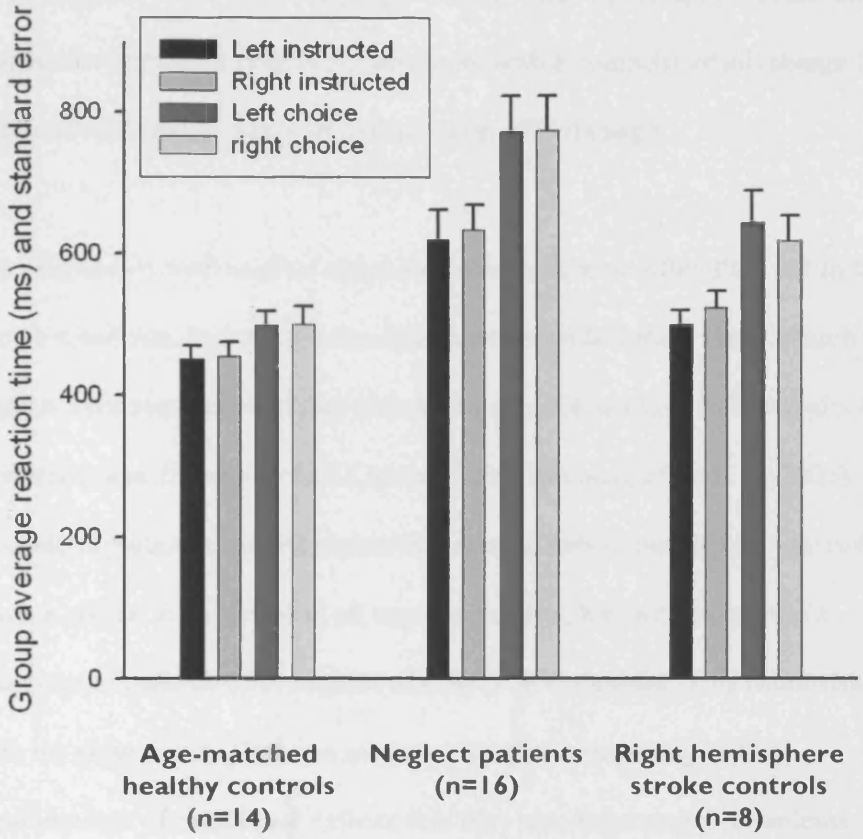


Figure 5.6 Reaction times for left and right instructed and freely chosen movements

Neglect patients were disproportionately slowed by the choice condition for *bo* leftward and rightward movements. There was a trend towards this tendency too i the non-neglect patients. Error bars shown standard errors of the mean.

(Ferber and Karnath 2001), although there may also be a lesion location association (Rorden, Fruhmann Berger et al. 2006). Crucially, parietal and occipital white matter damage was more common in patients with a *rightward motor bias* (in terms of making significantly more rightward movements) in the free choice condition (**Fig 5.5**), consistent with a competitive advantage for rightward movement plans in patients with PPC damage.

Not all patients with neglect chose to move right more often than left in the choice condition. Indeed, studies of eye movements during visual search in neglect have also revealed that patients may make as many left saccades as rightward ones (Niemeier and Karnath 2000; Mannan, Mort et al. 2005). A possible explanation for the rightward motoric bias in our experiment is that it is not a critical component in all neglect patients, but perhaps affects a subgroup of patients with neglect who have PPC damage. This is consistent with the view that neglect is a modular disorder comprising critical combinations of individual deficits that may also exist singly in patients without neglect on standard clinical tasks (Coulthard, Parton et al. 2007).

It is important to note that there are also other factors in our experiment that may have meant that rightward movement choice bias was underestimated in this free choice paradigm. The patients were instructed to move as fast as possible in one direction or another without making a plan in advance, with the aim that the movement was as automatic as possible and reflected competition between motor programmes. However, the experimenter is not privy to the decision processes that may be occurring within the patient. All the patients

had been informed of their diagnosis of neglect and would at some point have received therapy where they were prompted to use the left side or take into account objects on the left. This background may well have influenced the decisions made by neglect patients; it is possible they may have been actively trying to avoid making too many rightward movements.

Since this competitive bias in neglect patients *with right PPC lesions* occurred in the absence of any directional visual cues or lateralised spatial information, these data are consistent with a motoric deficit in these individuals. However, despite the central location of the stimuli, the response device and fixation, it is still possible that these patients with PPC damage manifest an attentional bias towards the right. Attentional processes have previously been thought to influence motor control (Punt, Riddoch et al. 2005). Thus one might argue that a covert attentional bias to the right influenced motor choice in patients with PPC damage.

However, if attentional bias to the right favours rightward motor programming, one might expect to see a directional speed difference in the instructed condition such that leftward instructed movements were slower than rightward in patients with a rightward movement choice bias. Contrary to this, there was no significant delay in initiating leftward movements in neglect patients with a rightward choice bias. In fact, three of these patients moved more quickly leftward than rightward in the instructed condition (**Fig 5.6**).

To probe further the motoric basis of the lateralised competitive bias found in patients with PPC damage, we used masked primes to modulate response choice in Experiment 2. Since, to a large extent, masked prime arrows are thought to influence motor rather than perceptual processing (Eimer, Schubo et al. 2002; Sumner, Nachev et al. 2007), if the lateralised response choice bias found in neglect patients is modulated by the presence of primes, one might have a stronger case that the basis of the rightward bias is motoric in neglect patients with damage to the areas of the PPC identified here (Sumner 2007).

5.3 Experiment 2

In this experiment, we specifically assessed neglect patients with PPC damage along with 10 normal controls using a masked prime paradigm (Eimer and Schlaghecken 1998) in order to gain further understanding of the basis of any directional bias in neglect patients. Interest lay in whether or not the directional bias was affected by interference from motor priming. Masked prime arrows are not visually perceived, but are thought to affect subsequent motor programming (for further details see **Chapter 1** and (Eimer and Schlaghecken 1998; Eimer 1999)).

The effect of prime arrows on a subsequent target is critically dependent on the interval between their presentation (stimulus onset asynchrony - SOA) (Eimer and Schlaghecken 1998; Eimer 1999). At short SOAs (<50ms), congruent prime arrows (those pointing in the same direction as the target), speed response initiation to the target. However at SOAs of around 150-200ms, there is paradoxical slowing of a target response when it is preceded by a congruent

prime, the negative compatibility effect (NCE). The NCE is though to result from automatic inhibitory mechanisms that prevent action on the basis of the irrelevant prime-induced response plan.

Evidence that such inhibitory processes act on *motor* programs rather than sensory representations comes from the finding of *effector-specific* prime effects. Eimer and colleagues have shown that left foot priming will not lead to inhibition of left hand movement (Eimer, Schubo et al. 2002). Further, a tiny medial frontal lesion that involves the supplementary eye fields but spares the rest of the supplementary motor area selectively interrupted inhibition of eye, but not hand movements (Sumner, Nachev et al. 2007). In contrast, a larger lesion involving more of the supplementary motor area, reversed automatic inhibition of both eye and hand movements (Sumner, Nachev et al. 2007).

Recent work has suggested interference from masked primes when subjects choose between two underdetermined response options, i.e. masked primes can bias 'free' choice (Schlaghecken and Eimer 2004; Kiesel, Wagener et al. 2006). The pattern of interference in the study by Schlaglacken and Eimer (Schlaghecken and Eimer 2004) was such that primes encouraged movement choice in the *opposite* direction, i.e. healthy subjects were more likely to choose to move right if the (previous) prime arrow pointed leftward and vice versa.

This paradoxical result occurred only when the mask and free choice stimulus were separated by 150ms and not when they were separated by 0ms. Such a

finding is the response choice analogue of the negative compatibility effect (NCE) found when subjects are required to respond to a target arrow following a prime (Eimer and Schlaghecken 1998; Eimer 1999). Thus, given enough time between prime and action cue, the brain has a bias for the *alternative* movement to that associated with the prime.

In the following experiment, subjects were asked to freely choose to move either right or left when they viewed a circle (**Fig 5.7**). The circle followed a masked prime that could be a rightward or leftward (arrow) or neutral prime (square). The separation of mask and prime was 200ms, an SOA found in previous studies to lead to a negative compatibility effect in the elderly population (Sumner, Nachev et al. 2007). It was expected that normal subjects would choose to move *left* more often than right when the free choice cue (circle) followed a *rightward prime*, and vice versa.

Five neglect patients, all with PPC damage, were tested on this paradigm. We expected that the pattern of prime interference on movement choice would illuminate the basis of a rightward bias, motor or sensory/attentional. Before further presentation of the task, we consider the possible outcomes of this experiment.

First, it was possible that the primes would have no effect on response choice in the patients with neglect. Previously it has been suggested that masked primes may not cause negative compatibility effects in elderly subjects who are slower to respond (Schlaghecken and Maylor 2005). Secondly it was possible

that directional bias in patients would be modified such that they made relatively fewer rightward movements when rightward primes precede the choice cue. This would be a similar pattern of behaviour to that expected in normal subjects, but perhaps with an alteration in baseline such that the patients made more rightward than leftward movements overall. This would not differentiate between attention and motoric causes of a rightward bias.

A third possible pattern of performance in the PPC neglect subjects would result from failure of the leftward motor plan to compete normally with the rightward motor plan, i.e. failure to inhibit rightward motor plans when activated by a right prime. This would be in keeping with the hypothesis generated in previous chapters that right PPC is critical for generation of competing motor programs, particularly leftward motor programs that inhibit rightward plans. In this case, one would expect more rightward movements to be made when a right prime precedes the choice cue, but no analogous leftward response bias with left primes. Such a pattern of interference in patients with PPC damage, or any reversal of the response choice NCE, would suggest that visuomotor prime processing relies on the PPC.

5.3.1 Methods

5 patients with neglect (**Table 5.2**), all with PPC damage, were tested along with ten normal controls on a free choice masked prime paradigm (**Fig 5.7**).

Age (years)	Time since stroke (months)	Bells R-L cancellation score	Line bisection (mm to the right)
Neglect			
73	96	4	26
78	3	4	15
58	38	3	-2
41	0.3	6	0
64	0.5	5	9

Table 5.2 Clinical information for free choice masked prime patients
Patients in red did not display rightward bias in neutral free choice condition

Subjects responded to a target stimulus that following a mask by 200ms (SOA 200ms) using the joystick. Pilot work and previous data has shown that elderly subjects have a negative compatibility effect at this SOA (Sumner, Nachev et al. 2007). There were 250 trials containing 5 different trial types in this paradigm. In 40% of trials, the target was an arrow stimulus that instructed the subjects to move left (20%) or right (20%), following a neutral (square) prime. These were the instructed trials. In a further 60% of trials, the target was a circle and subjects were free to move either left or right as fast as possible. In 1/3 of these trials, the prime was an arrow pointing left, in 1/3 the prime was a prime was an arrow pointing right and in 1/3 the prime was a neutral square. The instructed trials were included to limit the ability of the subjects to make a plan in advance about their direction of movement and also because previous work has suggested that unless prime arrows are relevant to the current 'task set' they will not influence performance (Schlaghecken and Eimer 2004).

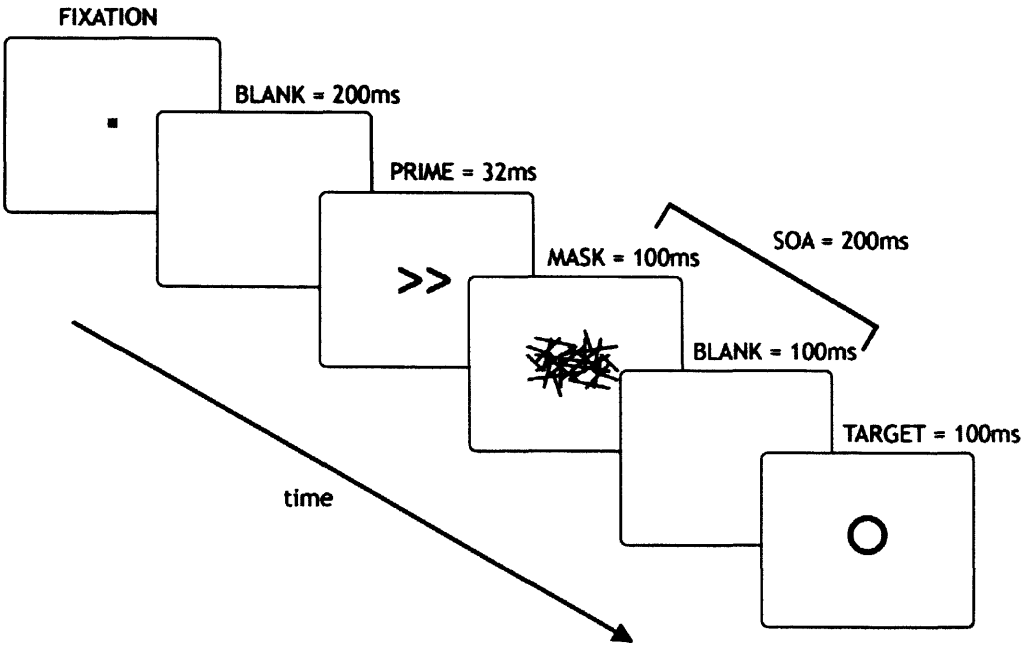


Figure 5.7 Free choice masked primes paradigm
Subjects were instructed to choose to move left or right as fast as possible when the circle target was presented (60% trials). This circle was preceded by either a left, right or neutral prime arrow. In the remainder (40%) of trials, subjects were instructed to move either left or right and the prime was neutral.

Circles were used as free choice symbols because they were symmetrical and carried no response association. Circles were chosen in preference to squares as the squares were already used as neutral primes preceding arrow stimuli in the instructed condition trials. Therefore, it is possible that on a trial-by-trial basis, the neutral cues carried a response association depending on the direction of the most recently viewed target arrow. Pilot investigation showed that prime arrow stimuli were not visible; subjects were unaware of their identity or presence. In addition, all subjects who participated in the final experiments were asked at the end of the practice block to describe what they had seen on the screen. Then again, at the end of the testing, subjects were asked if they had seen any arrows other than the ones following the hashed lines. None of the participants were aware of the arrow primes.

5.3.1.1 Data analysis

In the free choice conditions, subjects could choose either leftward or rightward movements. These data are represented as the percentage of rightward movements for comparison between groups. First an independent samples t test was performed on the movement choice data when primes were neutral for normal subjects versus neglect patients.

Thereafter, attempts were made to correlate neglect severity with rightward bias. As in the previous experiment, again Spearman's Rho non-parametric statistic was used.

Variation in response bias in leftward and rightward prime conditions was investigated using repeated measure ANOVA with the subject group as a between subject factor. Paired sample t-tests on the left vs right movement choice data for both groups were also performed.

Finally, median RT across all conditions was calculated for each subject. PPC neglect patients and normal controls were compared using an independent samples t-test as well as repeated measure ANOVA for leftward and rightward movements in 3 free choice conditions (prime types) and the instructed condition.

5.3.2 Results

Ten age-matched normal subjects and 5 patients with neglect and damage in the PPC completed this task (**Fig 5.8**). One normal subject was excluded from the analysis as she went left on >90% of all free choice trials, although apart from a leftward bias, she showed the same pattern of prime interference as all the other control subjects.

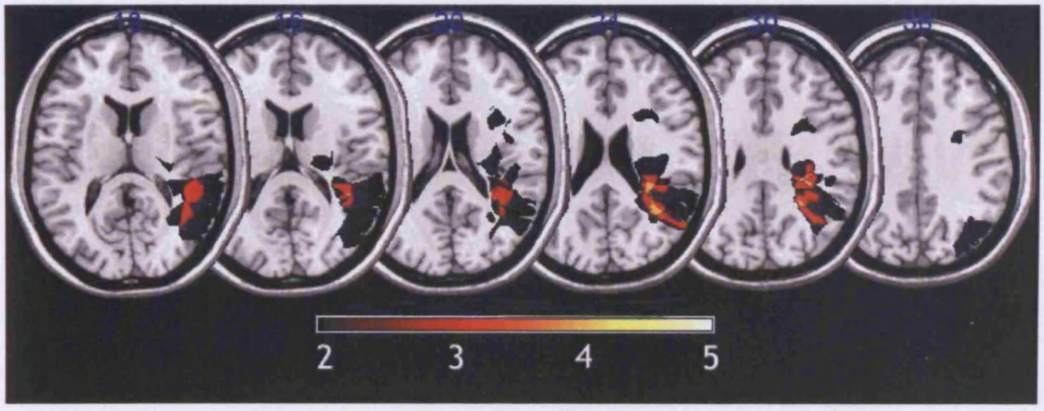


Figure 5.8 Lesion overlay for PPC neglect
All 5 patients had damage in the PPC with the maximum area of overlap being in the parietal white matter (yellow/white area).

The first question asked was whether or not neglect patients with PPC damage displayed a *rightward directional motor choice bias*. In the free choice condition with *neutral* primes, the healthy control subject group chose to move right 49.6% (SE 4.2%) of the time, whereas neglect patients with PPC damage moved right 54.4% (SE 11.4%) of the time. These were not significantly different and again there was considerable variability within the neglect group.

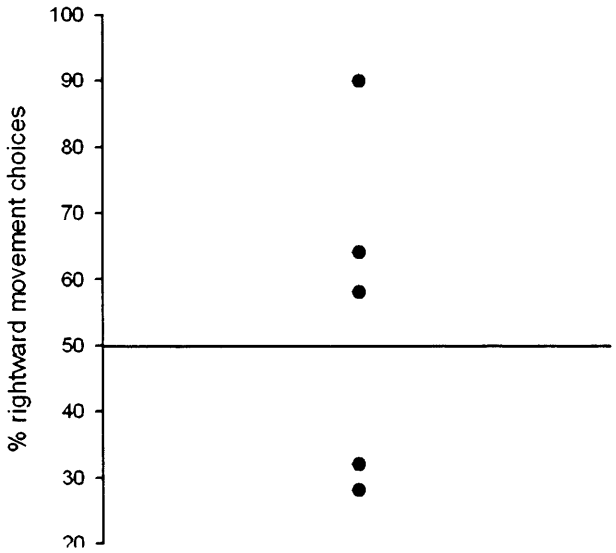


Figure 5.9 Percentage of rightward response choices when primes were neutral

Only 3 patients tended to move right more often than left. Due to the small numbers, the patients are considered as one group for further analysis.

Three out of 5 patients with PPC damage tended to move right more often than left in the free choice condition with a neutral prime (**Fig 5.9**). Although inferential statistics on such small groups (2 vs 3 subjects) have limited validity, patient demographics show that there was overlap in age and time since stroke between those who had a lateralised movement choice bias and those who did not (**Table 5.2**). Spearman's Rho correlation test of Bells Score (R-L cancelled) with right lateralised bias showed a trend towards a positive correlation (rho = 0.62, p=0.13, one-tailed).

Normal subjects were significantly more likely to choose to move left *after a right prime* and vice versa (paired-samples t–test on % rightward movements in left vs right prime conditions, t= 3.99, p<0.005). In other words, they displayed a response choice analogue of the NCE, with the prime movement direction being relatively inhibited.

Next we investigated whether motor priming in patients with neglect and PPC damage differed from that of normal controls (**Fig 5.10**). Repeated measures ANOVA revealed a highly significant interaction between subject group and prime type ($F(1,13)=24.361$ $p<0.001$). Thus rightward and leftward primes affect response choices differentially in PPC neglect patients (paired sample t-test significant difference between percentage rightward choices in right and left prime conditions $t=3.807$, $p<0.05$). Moreover, they affect results in the reverse pattern of priming from normal controls, i.e. consistent with lack of inhibition - but bilaterally (**Fig 5.10**). In patients, a right prime does not facilitate leftward choices – and vice versa – as in controls. Instead, right

primes increased the number of *rightward* response choices. Thus they do not show the normal inhibitory effect on response choices induced by directional primes.

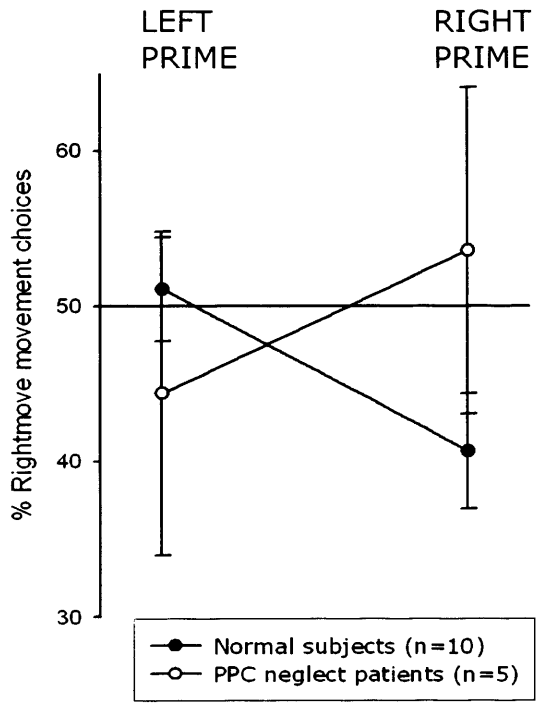


Figure 5.10 Percentage of rightward movements when primes were left or right arrows
Normal subjects choose to move right more often than left after a left prime and vice versa. Every single PPC neglect patient showed the reverse pattern of interference. So a right prime favoured a rightward movement whereas a left prime favoured a leftward movement.

One possible explanation for the difference between patients and normal controls could be that the patients are generally slower than normal controls and therefore the normal inhibitory mechanisms impact at a later stage of motor preparation (thus facilitating rather than inhibiting). However, independent sample t-test on the overall RT data showed no significant difference in response times between the PPC groups and the normal controls (t=0.604, NS **Fig 5.11**). In addition, repeated measure ANOVA on the median RT data showed no main effects of instruction type or interactions of instruction type and subject group.

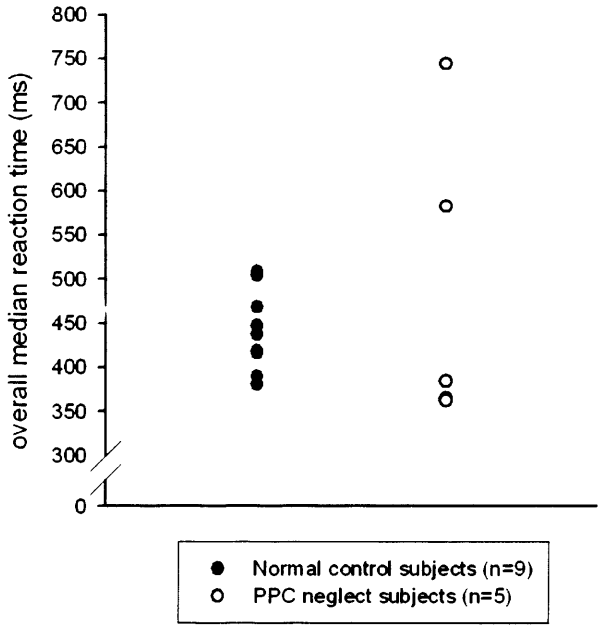


Figure 5.11 Median RTs for the normal controls and PPC neglect group
Overall, the patients were not significantly slower than the healthy control group.

5.3.3 Discussion of experiment 2

In this experiment, we tested neglect patients specifically with right PPC damage along with age-matched control subjects on a masked prime free choice task (**Fig 5.7**). Patients with PPC damage and neglect showed the *reverse* pattern of motor priming from normal subjects (**Fig 5.10**). Masked primes are thought to activate motor programs that are subsequently inhibited (Eimer, Schubo et al. 2002; Sumner, Nachev et al. 2007). Thus it appears that inhibition of prime-activated response plans does not occur normally in patients with PPC damage.

Can we tell why the effect of the primes is reversed in these patients? Data presented in chapters 3 and 4 have implicated the right PPC in processing of leftward directional motor programs selectively. However the findings reported here suggest that motor inhibition is abnormal for both rightward and leftward primes; rightward primes promote rightward response choices whereas leftward primes favour leftward response choices, the opposite pattern to normal controls. Therefore, evidence presented here suggests right PPC damage causes a non-lateralised motor deficit such that *inhibition* of the prime-activated plans does not occur whether they be rightward or leftward.
Such a reversal of prime-induced inhibition in patients with PPC damage is unlikely to result from attentional impairment, as attentional requirements are the same regardless of prime direction and the motor priming deficit is bidirectional, whereas attention in patients with neglect tends to be biased towards the right.

Is it definitely the motor program rather than the sensory representation that is inhibited abnormally in PPC neglect patients? Much previous work has suggested that automatic inhibition following masked primes occurs at the motor output stage of processing. As discussed earlier, this is because inhibition has been shown to be effector-specific (Eimer and Schlaghecken 2001; Eimer, Schubo et al. 2002; Sumner, Nachev et al. 2007). However, other accounts suggest that a proportion of the NCE results from mask-induced sensory representation opposite to that of the prime (Lleras and Enns 2004).

Could it be that patients with PPC damage and neglect actually have a perceptual deficit such that they fail to activate mask-induced sensory representations? Recent work demonstrates that prime-mask interactions, leading to mask-induced representation of the information opposite to the prime direction, account only for a small proportion of the NCE (Sumner 2008). In that case, contrary to the findings presented here, one would expect that if prime-mask interactions alone were impaired in PPC neglect patients, the patients would manifest the same pattern of behaviour as normal controls, but with a smaller magnitude. Another argument suggesting that the sensory representation of the prime was relatively preserved in these patients is that the primes did influence performance. Primes must have been processed and their meaning decoded, at least to some extent since patients' performance distinguished between right and left primes. Thus a sensory deficit in representation of the primes or the mask in our patients with PPC neglect appears unlikely.

It is also important to note that these patients were not any slower than normal controls overall. So we cannot explain the reverse pattern of prime effects in terms of generalised slowing of brain activity and a delay in automatic inhibition. Therefore these data imply that PPC is critical for normal automatic inhibition of *competing motor programs* when response choices must be made.

Here, a reversal of the expected NCE has been demonstrated in all five neglect patients with PPC damage when they make response choices. One further interesting question is whether or not these PPC neglect patients all have a reversed effect of priming when responses are *instructed*, such as in the paradigm presented in Chapter 4, rather than freely chosen. All the patients in this study also performed the instructed masked prime task (Chapter 4), always within a week of completing this free choice task. One patient had a significant *reversal* of the NCE when the target instructed the direction of movement, similar to the abnormality in response choice in this experiment (**Fig 5.12**). However, another patient, who had reverse prime effects in the free choice task (reverse NCE), was found to have a significant NCE when action was instructed, with the rest of the PPC neglect group having non-significant prime effects. In other words, *all patients* had a reverse effect of the primes when choosing a response, but the analogous, reverse NCE RT effect was not consistently present when responses were instructed.

How can we account for this discrepancy between prime effects in the *instructed* (**Chapter 4**) and *free choice* conditions in PPC neglect patients? Neither prime visibility nor response speeds can explain the difference in

patient performance between these two paradigms. It is possible that the performance of patients with right PPC damage actually indicates an important role for the parietal lobe in response selection when choices have to be made. Such a parietal function appears to be critical mainly when the response choice is underdetermined (free choice condition). This suggestion is consistent with functional imaging data showing parietal activations when responses are freely chosen, particularly when there are larger number of response choices (Jahanshahi, Jenkins et al. 1995; Lau, Rogers et al. 2004; Elsinger, Harrington et al. 2006; Mueller, Brass et al. 2007). They are also in line with the findings of a recent monkey neurophysiological study which demonstrated effector specific PPC neuronal activity when monkeys choose which responses they make (Cui and Andersen 2007).

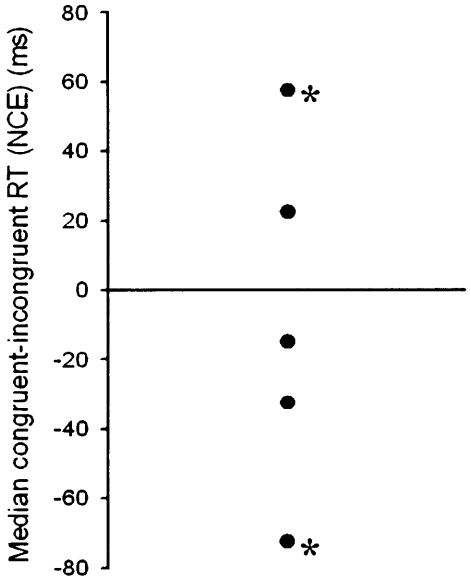


Figure 5.12 NCE data from chapter 4 for 5 PPC neglect patients
In contrast to response choice bias which was reversed in all PPC neglect subjects, there was greater variability in the RT following prime stimuli in the experiment described in chapter 4. One patient had a significantly reversed NCE whereas another had a significant *NCE*.

However, these data perhaps are at odds with recent evidence suggesting that right PPC mediates visually guided action whereas left PPC is involved in self-generated activity, which at first sight seems analogous to our free choice condition (Ogawa and Inui 2007). It is important to note that in our experiment, patients with right PPC damage were actively making a choice between two directions whereas in the work of Ogawa and Inui (Ogawa and Inui 2007), the left PPC appeared important for *monitoring* self-generated activity in a direction *instructed* by the experimenter. In any event, the data presented here raise the possibility of a role of the right PPC in response selection.

5.4 General discussion

The two experiments in this chapter sought to answer two questions: firstly whether or not the lateralised deficits found in neglect patients may be contributed to by a directional motor bias in response choice, and secondly whether the parietal lobe is critical for processing directional motor plans.

In neither experiment was there an overwhelming response choice bias to the right in patients with neglect, with or without PPC damage. However, in both experiments, there was a general trend towards rightward response bias in patients with neglect. In addition, rightward response bias correlated positively with the severity of neglect in experiment 1 (**Fig 5.4**). This suggests that a motoric bias to move rightward in preference to leftward could contribute to the neglect syndrome. However, it is clear that such a bias can still occur even in patients without neglect (**Fig 5.3**). Therefore it is likely that a rightward movement choice bias is only one component that may need to be accompanied

by other deficits, lateralised or non-lateralised, for a patient to manifest neglect on standard clinical tests.

Does parietal damage lead to a directional motor bias? Despite having many patients with large fronto-parietal lesions, the lesion analysis for experiment 1 suggested that posterior parietal cortex and white matter was damaged particularly in those patients with a rightward motor bias (**Fig 5.6**). While there was no significant rightward bias in the 5 patients with PPC damage and neglect in experiment 2, their response choices were abnormally perturbed by masked primes (**Fig 5.10**), which are considered to activate *motor* programs.

There are likely to be many factors that influence response choice even when subjects are instructed to move as automatically as possible without making a plan. Some patients may actively try not to move right too often as they have been told to avoid it during therapy sessions. Even normal subjects may impose criteria whereby, for example, they attempt to balance the overall proportions of leftward and rightward movements. Given this, it is remarkable how consistent the effect of the masked primes is within subject groups. In contrast to normal subjects, *every single patient* with PPC damage and neglect made more rightward movements following a right than a left prime (**Fig 5.10**). Motor priming appears to be one factor among many modulating response choice. PPC damage reverses the normal pattern of motor priming when subjects make a response choice. Therefore, overall, it does appear that the parietal lobe has a role in processing of directional motor choices and it is likely that PPC damage leads to a relative directional motor bias.

The functional role of the parietal cortex, whether motoric or purely sensory or attentional, has been controversial (Andersen and Buneo 2002; Bisley and Goldberg 2003). These data provide evidence for a role of the PPC in generation of motor programs, but there are also well described attentional, salience and stimulus-decoding properties within the PPC (Gottlieb, Kusunoki et al. 1998; Cavina-Pratesi, Valyear et al. 2006; Goldberg, Bisley et al. 2006). It may be that sub-regions of PPC subserve different functions (Rushworth, Krams et al. 2001; Husain and Rorden 2003) and act as an interface between perceptual inputs, coded in sensory frames of references, and outputs that directly activate distinct motor programs. Such a function is supported by the multiple frames of reference found in neurophysiological studies as well as responses modulated by perceptual, attentional, motoric and reward-based factors (Andersen 1995; Colby and Duhamel 1996; Andersen 1997; Colby 1998; Rushworth, Ellison et al. 2001; Andersen and Buneo 2002; Battaglia-Mayer, Caminiti et al. 2003).

In summary, we have shown that PPC damage leads to relative rightward directional motor bias even in the *absence of directional visual cues*. Thus one component deficit within the neglect syndrome appears to be rightward directional motor bias, although this deficit is not exclusive to neglect. Further, in patients with PPC damage and neglect, the effect of motor priming on response choice is reversed when compared to normal controls. This implies that the PPC normally subserves a motoric function, perhaps generating directional motor programmes that are subsequently inhibited, if not required.

Chapter 6: Asymmetric conflict adaptation in healthy subjects

6.1 Introduction

Using a variant of the Eriksen flanker task in chapter 3, a functional role for the right PPC in representing competing leftward response plans was identified. However, patients with left PPC damage did not show analogous deficits. They appeared able to represent competing rightward motor programs normally suggesting that there might be asymmetric representations for visuomotor control within the brain.

One possible explanation for such a difference between patients with left and right PPC damage is that the right hemisphere normally mediates *both* left and rightward motor programming, whereas the left hemisphere has a unilateral rightward function only. Therefore the right hemisphere can compensate for damage on the left side, but not vice versa. This would be analogous to proposals for the asymmetric control of spatial attention which has been suggested to be bilaterally represented in the right hemisphere, while the left hemisphere covers only the right side of space (Mesulam 1981). An alternative explanation is that leftward and rightward motor programs are processed identically, but the anatomical site of processing differs between hemispheres. For example, the right PPC may perform an analogous function to the left inferior frontal cortex.

Further evidence for an asymmetry in competing response programming comes from normal control data presented in chapter 3. While healthy subjects had

incongruence costs for both leftward and rightward movements, there was some asymmetry in the magnitude of these costs. Normal participants tended to have a greater cost for *leftward* than for rightward movements. This was significant when subjects used their right hands and trended toward significant even when using their left hands, suggesting the effect is direction, rather than effector, specific.

If leftward and rightward competing response plans are indeed represented asymmetrically in the brain, with two representations of competing rightward but not leftward plans, one might expect there would be differences in incongruence costs also with *adaptation* to one direction of movement. In other words, normal subjects may behave differently on incongruent trials in the context of predominantly left movement compared with when they move right repeatedly.

Here normal subjects performed a vertical variant of the Eriksen flanker task using only their right hands under three different conditions. In one condition, 80% of movements were leftward; in the second condition, 80% of movement was rightward; and in the third condition leftward and rightward movements were divided equally (50% each).

Previous variations of the Eriksen flanker task have varied the proportion of incongruent stimuli and shown that interference from incongruent information is dependent on context (Casey, Thomas et al. 2000; Scerif, Worden et al. 2006). When an incongruent stimulus is preceded by another incongruent

stimulus, the reaction time cost is less than when the preceding stimulus is congruent (Mayr, Awh et al. 2003). This reduction still occurs even when stimulus repetition is controlled for and therefore represents adaptation to the presence of response competition (Ullsperger, Bylsma et al. 2005). In this experiment, the proportion of movements in a given direction, rather than the proportion of incongruent stimuli, is varied in order to investigate how response competition may be modulated as a result of adaptation of neurons involved in visuomotor processing of one direction.

The specific hypothesis tested here is that repeated movements in one direction lead to alteration in the activity of neurons involved in sensorimotor representation of that direction. Therefore when 80% of movements are left, adaptation and perhaps attenuation of the neuronal response following leftward arrows would be expected, whereas rightward arrows would be relatively novel. Under these circumstances, incongruence costs due to rightward flankers (in the left incongruent condition) would be expected to be greater than those generated after leftward flankers (in the right incongruent condition).

In addition, if leftward and rightward competing response plans are represented asymmetrically in the brain – with two representations of competing rightward but not leftward plans – one might expect the reduction in incongruence costs due to adaptation to be less for leftward flankers (when 80% of movements left) than rightward flankers (when 80% of movement right).

6.2 Methods

Ten healthy subjects were recruited to participate in this variation of the Eriksen flanker task (all right-handed, 6 female, average age 61.7, range 29 – 76 years). The paradigm was similar to that used in chapter 3 except that the proportion of rightward and leftward movements varied between sessions. Subjects responded using a centrally placed joystick either leftward or rightward according to a central target arrow. All stimuli were in the vertical midline.

In this paradigm the proportion of movements in each direction was modified between testing sessions (**Fig 6.1**). In the predominantly left session 80% of movements were left (consisting of 70% neutral flanker, 5% incongruent flanker, 5% congruent flanker trials). The rest of the trials (20%) were rightward movements (consisting of 10% neutral flanker, 5% incongruent flanker, 5% congruent flanker trials).

In the 50/50 session there were equal numbers of leftward and rightward movements (1/3 neutral, 1/3 incongruent and 1/3 congruent).

In the predominant right session 80% of movements were rightward (70% neutral flanker, 5% incongruent flanker, 5% congruent flanker) and 20% were left (10% neutral flanker, 5% incongruent flanker, 5% congruent flanker).

Note that these proportions mean that even when there were far more movements in one direction than another, the *same* number of incongruent and

congruent trials occurred in either direction. Figure 1 displays the trial types and their percentages graphically.

In the 50/50 condition, subjects performed 6 blocks with 36 trials in each giving 36 trials in each condition. For the predominantly left and right conditions, the subjects performed 18 blocks of 40 trials giving 36 trials in the incongruent and congruent conditions for each direction and 504 neutral in the predominant direction and 72 neutral in the non-predominant direction. Therefore congruent and incongruent reaction times are used for directional comparisons with neutral data provided for reference only.

The order of the testing sessions was counterbalanced across individuals and each session was separated by a week to avoid any hang-over priming effect.

6.3 Results

As expected, subjects were slower in the incongruent than neutral or congruent conditions for both rightward and leftward movements across all three conditions. Repeated measure ANOVA on the median RT data with condition (80% left vs 80% right vs 50/50), direction of movement (left vs right) and flanker type (incongruent vs congruent) as within subject factors showed a significant reaction time cost with incongruent flankers (main effect of flanker type $F(1,9)=19.588$, $p<0.005$, incongruent significantly slower than congruent overall, pairwise comparisons mean difference incongruent vs congruent = 65ms, $P<0.05$, **Fig 6.1**).

There was also a main effect of *predominant direction* condition, i.e., whether subjects were making leftward and rightward movements equally or predominantly leftward or rightward ($F(2,18)=10.446$, $p<0.005$). Reaction times in the 50/50 condition were faster than those in the other two conditions (post hoc pairwise comparisons show significant difference between 50/50 and both other conditions: mean difference 35.5ms ($p<0.01$) and 35.6ms ($p<0.05$) after Bonferroni correction for 80% left and 80% right conditions respectively). However, there was no *main* effect of movement direction; overall rightward and leftward directional response times were similar.

Incongruence costs varied with the proportion of movements in each direction. They were greater for leftward movements when 80% of actions were left-directed and greater for rightward movements when 80% of movement were right-directed compared to the 50/50 condition. In addition baseline response speed (neutral and congruent conditions) tended to be faster in the *predominant direction*. The ANOVA revealed a 3-way interaction between predominant direction, direction of movement and flanker type ($F(2,18) = 13.3$, $p<0.001$). Next the source of this interaction is investigated.

From **Figure 6.1** it can be seen that the increase in incongruence costs *in the predominant direction* was symmetrical.[1] However, crucially, there was a

[1] It should be noted that this does not simply result from a reduction in the baseline (congruent) RT in the predominant direction (repeated measure ANOVA on the incongruent RTs alone for the predominant direction and the 50/50 condition leftward and rightward revealed a main effect of experiment type – incongruent RTs were slower in the predominant direction (whether that is leftward or rightward) than for the corresponding direction in the 50% condition ($F(1,9)=13.2$, $P<0.005$) – no interactions).

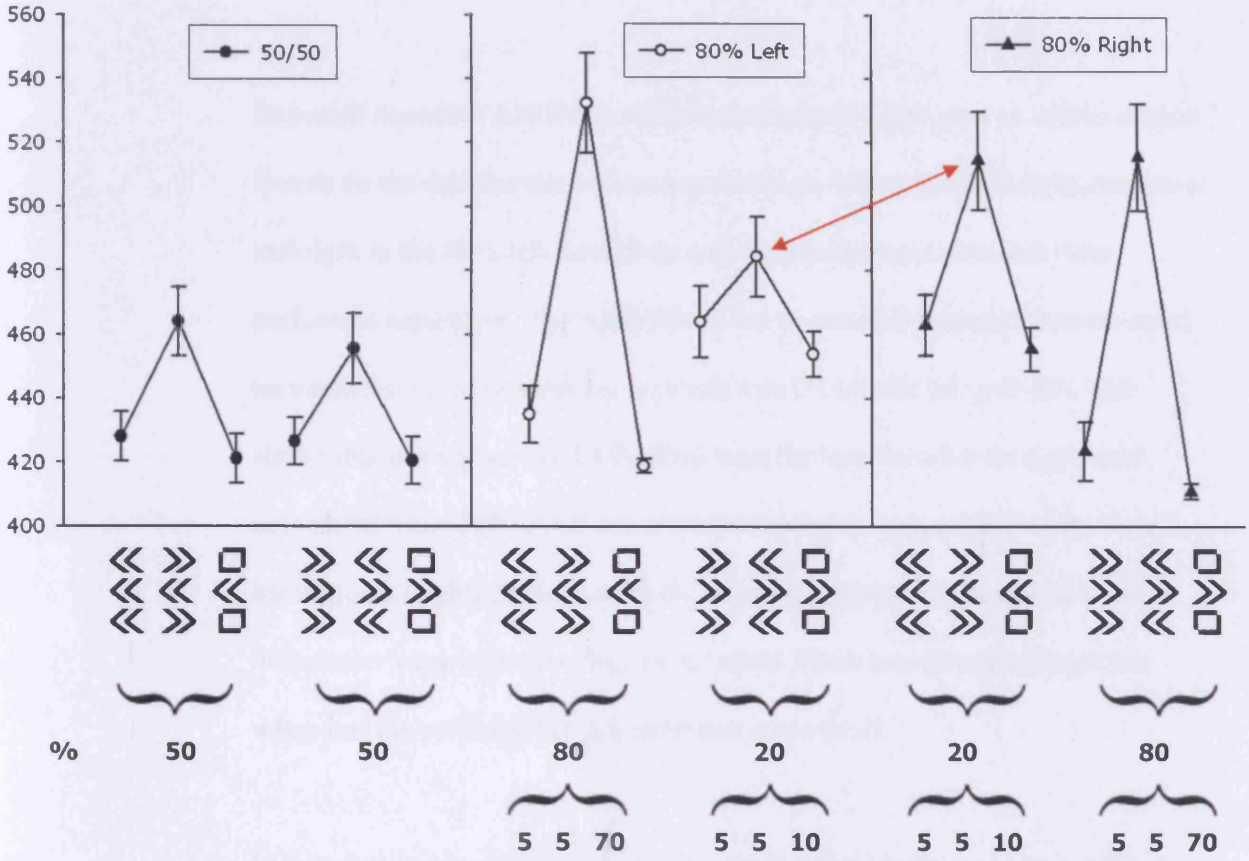


Figure 6.1 Median RT data in all three conditions
Median RTs in the 50/50 condition revealed a cost of incongruence, similar for both leftward and rightward movements. If one first looks at the congruent and neutral reaction times in the 80% left and 80% right conditions, it is obvious that subjects were generally slower in the uncommon direction. If then incongruent RTs are considered, they are all similar except the right incongruent RT in the 80% left condition (red arrow). Leftward flankers engender the incongruence in this trial-type. Therefore, repeated movements leftward cause neuronal adaptation such that the leftward flankers no longer interfere with the rightward RT. However, the same adaptation does not occur for the rightward flankers; the incongruent RT is similar in the 80% right condition both leftward and rightward.

significant asymmetry in the effect of the incongruent flankers *in the uncommon direction* (denoted by the red arrow figure 1).

Repeated measures ANOVAs with flanker type and direction as within-subject factors on the data for the uncommon direction (left in the 80% right condition, and right in the 80% left condition) and the predominant direction were performed separately. The ANOVA on the uncommon direction data revealed an interaction between flanker type and side ($F(1,9)=6.981$, $p<0.05$). This shows that incongruent (left) flankers were far less intrusive for rightward movement *when 80% of all movements were left* (average 20ms cost), than incongruent (right) flankers were for leftward movement *when 80% of all movements were right* (average 51 ms cost). There was no such interaction when just the predominant direction was considered.

In summary, when 80% of movements were leftward, the incongruent RT due to leftward flankers was reduced compared with the incongruent RT due to the rightward flanker (paired samples t-test $t= 2.687$, $p<0.05$). However, when 80% of movements were rightward, the incongruent RT was similar for both leftward and rightward flankers ($t=0.41$, $p=0.968$). Therefore the adaptation effect of repeatedly moving in a given direction affects leftward flankers significantly more than rightward flankers.

6.4 Discussion

Ten healthy subjects were tested on a modified Eriksen flanker task. In one session they were required to move left 80% of the time; in a second session, they moved in each direction an equal number of times; and in a third session they moved right 80% of the time. We showed that varying the proportion of movements in a given direction not only affected baseline response times, but also modulated the impact of incongruent flankers. Crucially, that effect differed according to whether the flankers were leftward or rightward.

While the impact of leftward flankers was reduced by repeated leftward movement, the incongruent RT for rightward flankers was not significantly affected by repetition (Figure 1). This suggests that rightward and leftward competing motor programs are indeed processed differently in the brains of normal individuals. It appears that rightward competing motor plans are far more robust than leftward, in keeping with the finding in chapter 3 of larger incongruence cost for leftward than rightward movements in normal subjects.

Alternatively one could suggest that lack of modulation of right flanker effects implies that right arrows or motor programs do not have a distinct processing channel. However, this is made very unlikely by the finding that when no adaptation had taken place (the 50/50 condition), the reaction time costs were similar for rightward and leftward flankers suggesting that both right and left flankers were processed distinctly from incongruent target arrows. Therefore, rightward flankers are processed, but it appears that neurons processing

rightward flankers do not 'fatigue' in the same way as those propagating leftward visuomotor representations.

This is consistent with the suggestion that rightward response plans are represented in both leftward and rightward parietal cortices, whereas leftward response plans are represented only in the right PPC. These data make it very unlikely that rightward and leftward competing response plans are processed in exactly the same way. However, they do not distinguish the possibility that rightward competing response plans are represented in the left PPC and somewhere other than left PPC (e.g. right PPC) from the possibility simply that the way in which rightward and leftward response plans are processed is mechanistically different.

Is the change in RTs following repeated movements in a given direction due to sensory or motor adaptation? When 80% of movements are left, the subjects make four times as many movements to the left as to the right. In addition subjects see leftward arrows in either the target or the flanker position on 85% of trials and rightward arrows on only 25%. Therefore the results here could reflect either sensory or motor adaptation. Possible future experiment could distinguish between these two possibilities by using an arbitrary response association (e.g. coloured square) to indicate leftward or rightward in the neutral condition. That way, the number of leftward and rightward arrows seen would be balanced in the 80% left and 80% right conditions as they would only be viewed in the incongruent and congruent conditions.

Why are rightward and leftward competing response plans represented differently? Could it be that the asymmetry is somehow protective: one inhibits movements leftward with the right arm more than those that rightward because leftward movements could result in a collision with one's own body? This is possible, but a similar asymmetry trend was also suggested by the data collected from normal controls using their left hands where a leftward movement would actually be away from the body (chapter 3). Alternatively, it could be defensive – rapid rightward movements with the right hand may more commonly be required to protect the body.

Although any explanation for this asymmetry is speculative, three different data sets presented in this thesis – the Eriksen flanker paradigm performed by normal subjects, the right and left PPC Eriksen flanker data and the effect of priming by repeated movements described above – all suggest that competing rightward motor programs are processed differently from leftward in the human brain.

Perhaps such asymmetry is not surprising given the large body of evidence suggesting hemispheric specialisation for motor control (Serrien, Ivry et al. 2006). It has been proposed that hemispheric lateralisation may be evolutionarily beneficial to prevent interhemispheric competition for simple processes that need only one site (Toga and Thompson 2003). Here we have found evidence for asymmetry in processing competing directional motor programs. Data presented in chapter 3 suggests that right PPC is critical for resolving competition between directional visuomotor plans and previous

functional imaging work has shown right inferior parietal activation when responses compete (Botvinick, Nystrom et al. 1999; Casey, Thomas et al. 2000). However, lesions of right PPC reduced the impact of leftward competing motor programs only leading to the proposal that rightward motor programs are also represented elsewhere. Such redundancy in the nervous system is perhaps the outcome of lateralisation of functions that were bilateral and symmetrical in primitive animals. While one structure may adapt to perform a bilateral function, there may be some residual activity in the other hemisphere subserving a unilateral function only.

However, although asymmetry is well described, it is the left rather than the right hemisphere that has previously been considered dominant for motor control (Kimura and Archibald 1974; Buxbaum, Kyle et al. 2006). Patients with lesions involving the left hemisphere have difficulties with skilled movements, apraxia, as well as speech disturbances (Kimura and Archibald 1974; Blank, Scott et al. 2002; Buxbaum, Kyle et al. 2006). Left hemisphere dominance for speech and motor control is thought to be closely linked to right handedness (Serrien, Ivry et al. 2006). In contrast, unilateral spatial neglect and motor neglect of the contralesional limb are common in patients with right hemisphere damage and ipsilateral motor control deficits following right hemisphere stroke are less obvious clinically ((Buxbaum, Ferraro et al. 2004) **see introduction**). The findings in this thesis suggest that while the left hemisphere may well subserve some aspects of skilled movement, the right hemisphere is dominant for resolution of competition between ballistic directional motor plans. Perhaps only by focussing on specific subcomponents

of motor processing under defined circumstances can such hemispheric specialisation be identified.

Chapter 7: Motor neglect associated with loss of action inhibition

7.1 Introduction

Motor neglect, underuse of one side of the body not explained by weakness or sensory less, occurs either in isolation or as part of the neglect syndrome (Valenstein and Heilman 1981; Laplane and Degos 1983), complicating around 36% of all stroke cases (Siekierka-Kleiser, Kleiser et al. 2006). Attempts to understand and successfully treat the condition have been hampered by diagnostic difficulty as it often coexists with hemiparesis (Punt and Riddoch 2006). Indeed, to the best of our knowledge, there are no reports of behavioural studies conducted on this disorder beyond clinical, observational descriptions.

Neurophysiological evidence implicates failure to modulate inhibition of the primary motor cortex in patients with motor neglect. Transcranial magnetic stimulation (TMS) at 1.5 times the resting motor threshold leads to a silent period of approximately 180 ms in the surface electromyography (EMG) of tonically activated small hand muscles. This silent period, which is considered to be due to cortical processes, is prolonged in the ipsilesional small hand muscles of stroke patients with motor neglect (Classen, Schnitzler et al. 1997). However, the behavioural impact of these findings has never previously been investigated.

Here we probe the inhibitory processes involved in motor neglect behaviourally using a masked prime task which offers an important window

onto automatic inhibitory control (Eimer 1999). This paradigm has recently been deployed to probe deficits in Parkinson's disease as well as focal lesions of supplementary motor areas (Seiss and Praamstra 2004; Sumner, Nachev et al. 2007). In this task, prime arrow stimuli are presented for less than 50ms and then masked **(Fig 7.1)**. Normal observers are not able to report having seen the prime. However, the prime influences performance when a subsequent target arrow requires a response (Eimer, 1999).

Unlike classical priming effects where similarity (congruence) between prime and target *speeds* response, if the interval or stimulus onset asynchrony (SOA) between mask and target is 100-200ms, there is a paradoxical *delay* in reaction time (RT) when the prime and target are congruent – so-called negative compatibility effect. Thus motor programs evoked by the prime are inhibited if they do not continue to response initiation within ~ 100ms. Further, at these crucial SOAs (100-200 ms), there is facilitation when prime and target point in *different* directions (incongruent condition).

Why does automatic *inhibition* of response plans occur? At any one time, we are confronted by a host of possible response alternatives to stimuli in the environment. In fact, remarkably, simply looking at an object may be sufficient to automatically and unconsciously activate motor plans to grasp it (Humphreys 2001). Such 'priming' is useful when we need to act quickly, but what if we don't want to perform the primed action? Clearly, flexible control over our actions requires the ability to inhibit action priming so that we can

make other choices. Such flexible control may paradoxically occur automatically (Sumner, Nachev et al., 2007).

The negative compatibility effect is thought to probe brain mechanisms responsible for automatic inhibition of *unwanted* action plans. In the masked prime task, such unwanted, but automatic response plans are generated by prime arrows. Exactly how these plans are classified as "unwanted" is unclear (Eimer 1999), but one possibility is that primed action plans are automatically inhibited if they do not develop further towards movement execution within 100-200 ms. Such inhibition allows alternative action plans to be made, permitting flexible control over behaviour. In fact, the mask prime task shows that at 100-200 ms after a prime (say right arrow), the alternative or incongruent movement (left response) is actually facilitated. Here we ask whether this is also the case in patients with motor neglect.

A possible analogy could be drawn between the negative compatibility effect and *inhibition of return* described in the visual attention domain, where orientation of attention back to areas recently visited is delayed (Posner, Rafal et al. 1985). In normal individuals, inhibition of return has been suggested to ensure efficient visual search, preventing returns to previously searched locations. Lateralised breakdown of inhibition of return has been shown in patients with visual neglect (Lupianez, Decaix et al. 2004). We investigated whether deficits in automatic action inhibition might underlie motor neglect.

We hypothesized that motor planning for the left arm is intruded upon by conflicting movement plans for the right arm in right hemisphere patients with motor neglect. In other words, we expect that in patients with left motor neglect, irrelevant right primes will slow – not facilitate – movements of the left arm. In addition we investigate which parts of the brain are associated with such asymmetric motor inhibition and motor neglect.

7.2 Methods

Seven patients with and six without motor neglect following right-hemisphere stroke were examined along with ten age-matched healthy controls **(Table 7.1)**. All subjects gave informed consented with local ethics committee approval.

Motor neglect was diagnosed clinically on the basis of subjective complaint by the patient or care-giver of under-use of the left side in the absence of significant sensory loss, weakness, apraxia or ataxia. Since it can be difficult to differentiate limb weakness from motor neglect, we specifically excluded patients with weakness on formal neurological examination at the time of experimental testing.

Note that for our purposes we make the pragmatic distinction between motor neglect and paralysis on the basis of clinical examination. It is possible that severe motor neglect may manifest as paralysis but this study specifically did not include such patients. In addition, motor neglect patients all displayed breakdown of alternating hand movements, i.e. they were particularly impaired when asked to open one fist as they closed the other repeatedly.

We also developed an objective clinical measure of motor neglect severity based on the number of times each patient opened and closed his fist in one minute using each hand separately, and both hands simultaneously with eyes closed (**Table 7.1**).

Patients were positioned approximately 100cm from a 15" Sony Vaio (PCG-5A1M) laptop screen where stimuli were presented centrally using Presentation (Albany, USA) software. A central prime stimulus was presented (32 ms) and subsequently masked, rendering the prime imperceptible (**Fig. 7.1**). A speeded button press response with either the left or the right hand (Cedrus button-box, San Pedro, USA) was required to the target arrow that followed the mask after 200 ms (SOA). To ensure the prime was successfully masked, all subjects were asked firstly to describe what they saw after the first block and then, at the end of the experiment, if they saw any arrows other than the ones following the hashed lines (mask), and none did.

There were 12 blocks of 24 stimuli each containing 6 different trial types randomised with the constraint that each trial type occurred the same number of times per block. Therefore there were 48 data points for each trial type.

The Brunner-Munzel rank order test (www.sph.sc.edu/comd/rorden/mricron/) was used to investigation brain areas associated with abnormal behaviour. This is a relatively assumption free lesion analysis method in which continuous data are used to identify brain regions where damage correlates with impaired

performance **(Fig 7.4b and c)**. This test was performed on lesion maps taken from the routine clinical imaging of all 13 stroke patients. At a given voxel, the average ranking on the behavioural measure in question of patients with lesions was compared to the ranking of those without damage at that voxel.

In order to increase statistical power, only voxels where at least 3 subjects had a lesion were included in the analysis. This technique was used to identify areas associated firstly with abnormal performance in our experimental test and secondly with increasing severity of motor neglect (combined motor neglect score). Bonferroni correction was applied (post-correction significance level of $p<0.05$).

Description of symptoms	Age	Time since stroke (months)	Bells score *	Line bisection score (mm rightward)	Personal neglect score **	Tactile neglect N/Y	Combined motor neglect score
Family noticed lack of movement on left side during daily activities	53	2	0	2	0	N	41.4
Difficulty walking **due to 'leaving left leg behind'. Finding** arm hanging in uncomfortable positions and not being involved in activity particularly mobile phone use and eating	67	0.5	2	4	0	N	53.7
Absolutely no spontaneous activity in left arm unless prompted. Also great difficulty walking and wheel chair use dangerous as forgets to use one arm. Anosognosic.	61	1	5	15	2 (left side)	Y	99.8
Difficulty with two-handed activity particularly eating and failure to move left hand noted by physiotherapist	69	1	0	3	0	N	22.8
Clumsiness reported by patient and friend. Limited spontaneous movement of hand noticed when writing.	66	1	0	0	0	N	123.8
Complete failure to use the left hand except when prompted.	78	2	6	18	0	Y	16.1
Avoided using left hand except when prompted. Difficulty with make-up reported by patient.	36	2	0	-2	0	N	20.7

Table 7.1 Subjects details

Motor neglect was assesses by uni- and bimanual motor neglect scores (summed to give the combined motor neglect score) that reflect the difference between the number of left and right-handed movements in each condition:

$$\frac{(R-L)\ x100}{(R+L)}$$

where R=number of right hand movements and L =number of left hand movements. Fist opening is defined as > 90^{o} movement of the long axis of the second phalanx). Non-motor neglect patients: performance range on combined motor neglect score -17 to 6.69 (average -1.71, SD 8.96); mean age 53.5 (range 44-71 years), none had significant weakness. It is important to note that there has been confusion in the literature about the term motor neglect, with some authors using it to describe other movement deficits following stroke including directional impairments with the ipsilesional limb. However, many investigators now use the diagnostic label "motor neglect" to refer to the syndrome described here of under-use of the contralesional limb.

* Bells cancellation score (number of right-sided – left-sided cancellations)
** Personal neglect - Modified fluff test (Cocchini, Beschin et al. 2001) (8 post-it notes attached to patient's body while blindfolded, patient was required to remove all post it notes, score reflects number missed).

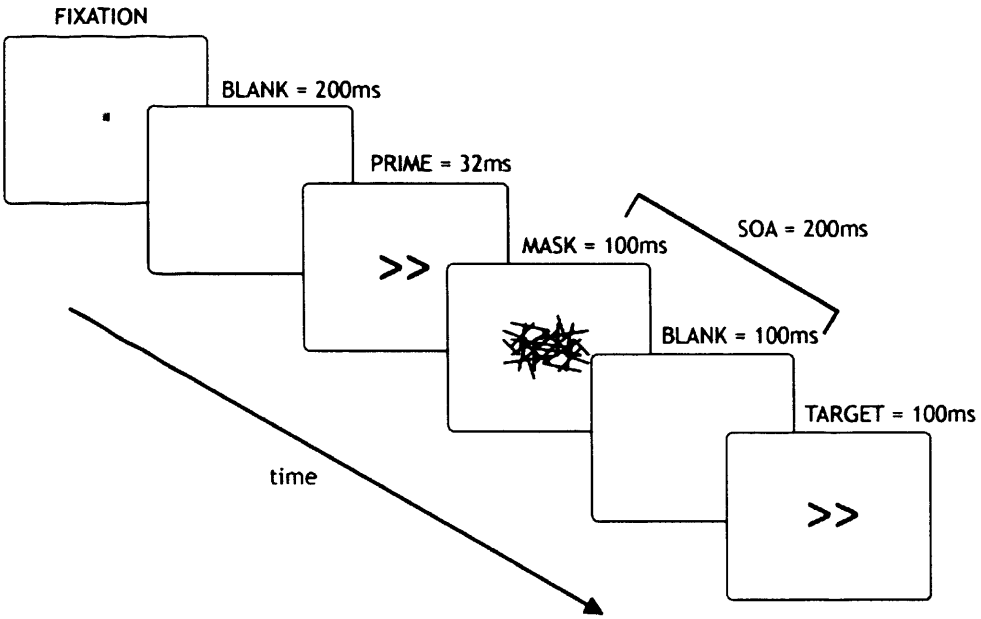


Figure 7.1 Masked prime paradigm
Subjects performed a masked prime task (a). Arrow stimuli subtended approximately 1.5 x 1 degrees. Neutral primes comprised the arrows rearranged forming a square that carried no directional information (not shown). 12 blocks of 24 stimuli contained six different trial types randomized with the constraint that each condition occurred the same number of times per block. Hands were covered during the experiment to prevent visual guidance of movement. Subjects were instructed to fixate the laptop display centrally and eye position was monitored by the experimenter. A practice session (< 2mins) took place beforehand.

7.3 Results

Our primary aim was to investigate the effect of *incongruent* primes, specifically selective intrusion of right hand motor plans (evoked by the prime) onto left hand movements (right prime followed by left target arrow = left incongruent condition). Secondly, we explored whether *congruent* primes resulted in RT slowing for left and right hand movements in patients with motor neglect, as expected in normal subjects.

As hypothesized, every single patient with motor neglect was delayed when a right prime preceded a leftward movement, i.e., in the left incongruent condition **(Fig 7.2)**. In contrast, age-matched and stroke control groups showed the expected standard small benefit of incongruent primes bilaterally and no significant effect of the prime respectively (3 way interaction: subject group X response side X prime type ($F(4,40)= 4.772$, $p<0.005$). Thus, motor neglect patients showed a complete reversal of the incongruent prime interference pattern found in normal controls for left hand movements only.

Motor neglect patients were slower than either control group even with the ipsilesional limb. Critically, however, there was no significant difference between the left and right hand overall response speeds in the motor neglect group. Therefore, the lateralized inhibitory deficits do not simply result from left-sided slowing. Generalised slowing is a well-described finding in patients with right hemisphere stroke, potentially explained by attentional failure (Howes and Boller 1975). Patients without motor neglect may have performed

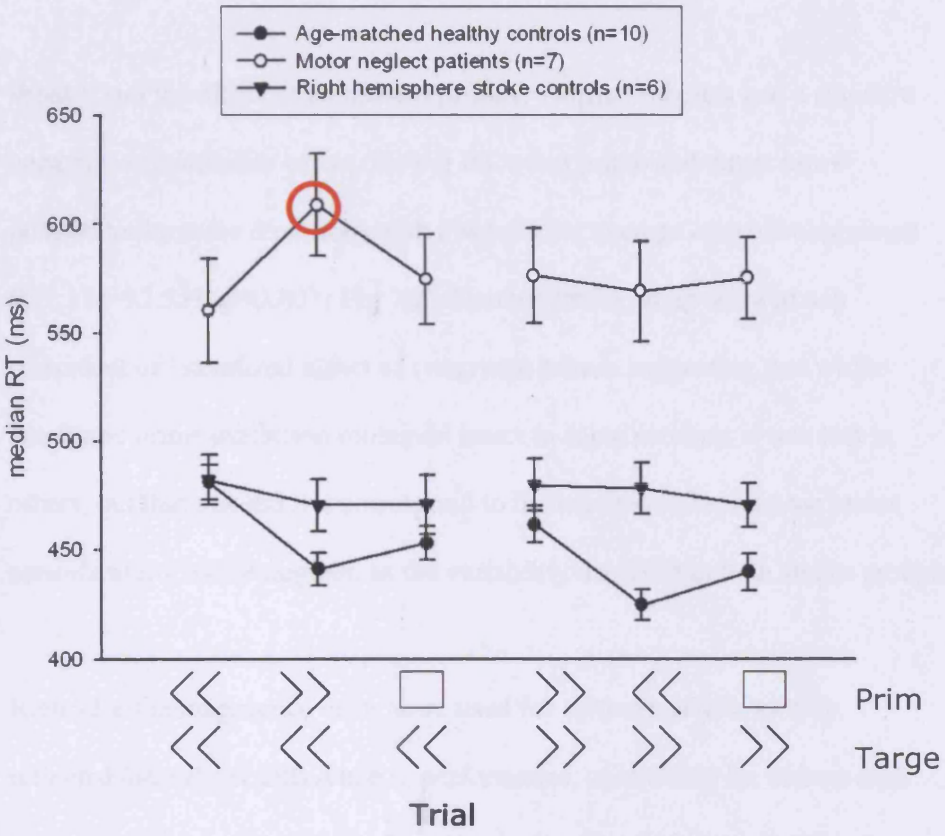


Figure 7.2
Only motor neglect patients showed significant RT delay when a right prime preceded a movement with the left hand (red circle). So right hand motor plans significantly intrude on left hand movement, but not vice versa, in motor neglect patients only.

faster perhaps because either their lesions were relatively small or did not include regions involved in attentional processing.

What about the effect of *congruent* primes? Normal subjects had a standard negative compatibility effect (slower RT when prime and target arrow pointed in the same direction) with a significant average *cost* of congruence ($F(2,18)=32.539$, $p<0.001$; **Fig 7.2**). Neither stroke group showed any consistent or lateralized effect of congruent primes suggesting that while automatic prime inhibition remained intact in some patients, it was lost in others, but that this did not correspond to the behavioural syndrome under consideration, motor neglect, as the variability occurred in both stroke groups.

Right- Left incongruence costs were used for further analysis as they reflected *lateralized* difference in performance, controlling for factors such as age or slowness that could affect prime interference bilaterally (Seiss and Praamstra 2004). This experimental measure correlated significantly with the behavioural motor neglect severity score (Spearman's Rho 0.555, $p<0.05$ - **Fig 7.3**).

Brunner Munzel analysis on the (Right – Left) incongruence cost for all 13 patients showed that right putamen and subcortical white matter were significantly more likely to be damaged in patients with intrusion of right hand motor plans onto leftward movements **(Fig 7.4b)**. Indeed, two of our motor neglect patients with small strokes involving the putamen both demonstrated a cost of incongruence for left movements only, just like

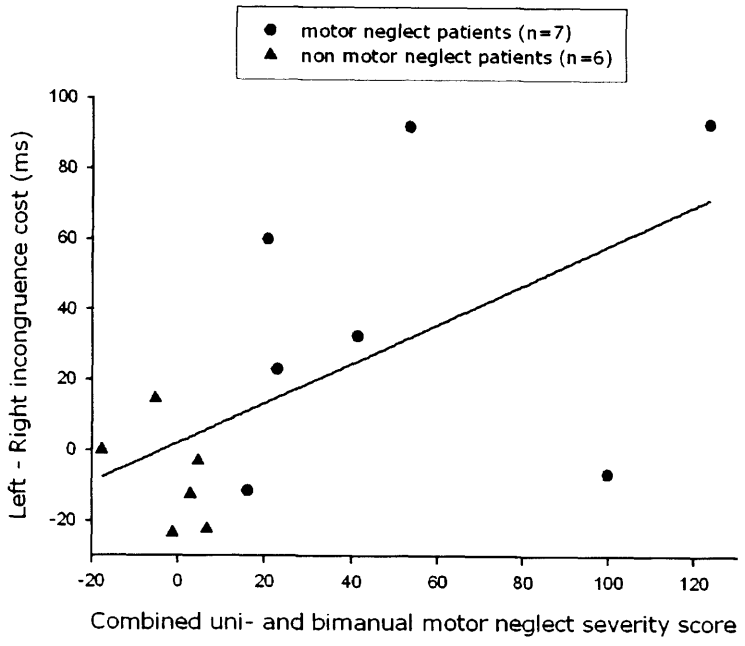


Figure 7.3 Correlation between motor neglect severity and left incongruence cost.

patients with larger lesions. In addition, close inspection of individual lesions revealed that all patients with motor neglect had lesions that involved the putamen, although the area of putamen involved differed between individuals.

We were also interested in how many patients with motor neglect had lesions involving the thalamus. Thalamotomy, a procedure used to treat dyskinesia, has previously been shown to result in motor neglect (Vilkki 1984). Two of our patients had lesions that incorporated much of the thalamus and one patient had a lesion that encroached onto the ventral part of the thalamus.

Further lesion analysis looking at areas associated with behavioural motor neglect was performed using the Brunner Munzel test, this time on the combined neglect severity score **(Table 7.1)**. Several small regions were significantly associated with motor neglect including a region close to the putamen similar to that described above **(Fig 7.4c)**. Given the relatively small number of patients in the analysis and scattered areas associated with severe motor neglect, we feel inference from this lesion analysis should be cautious.

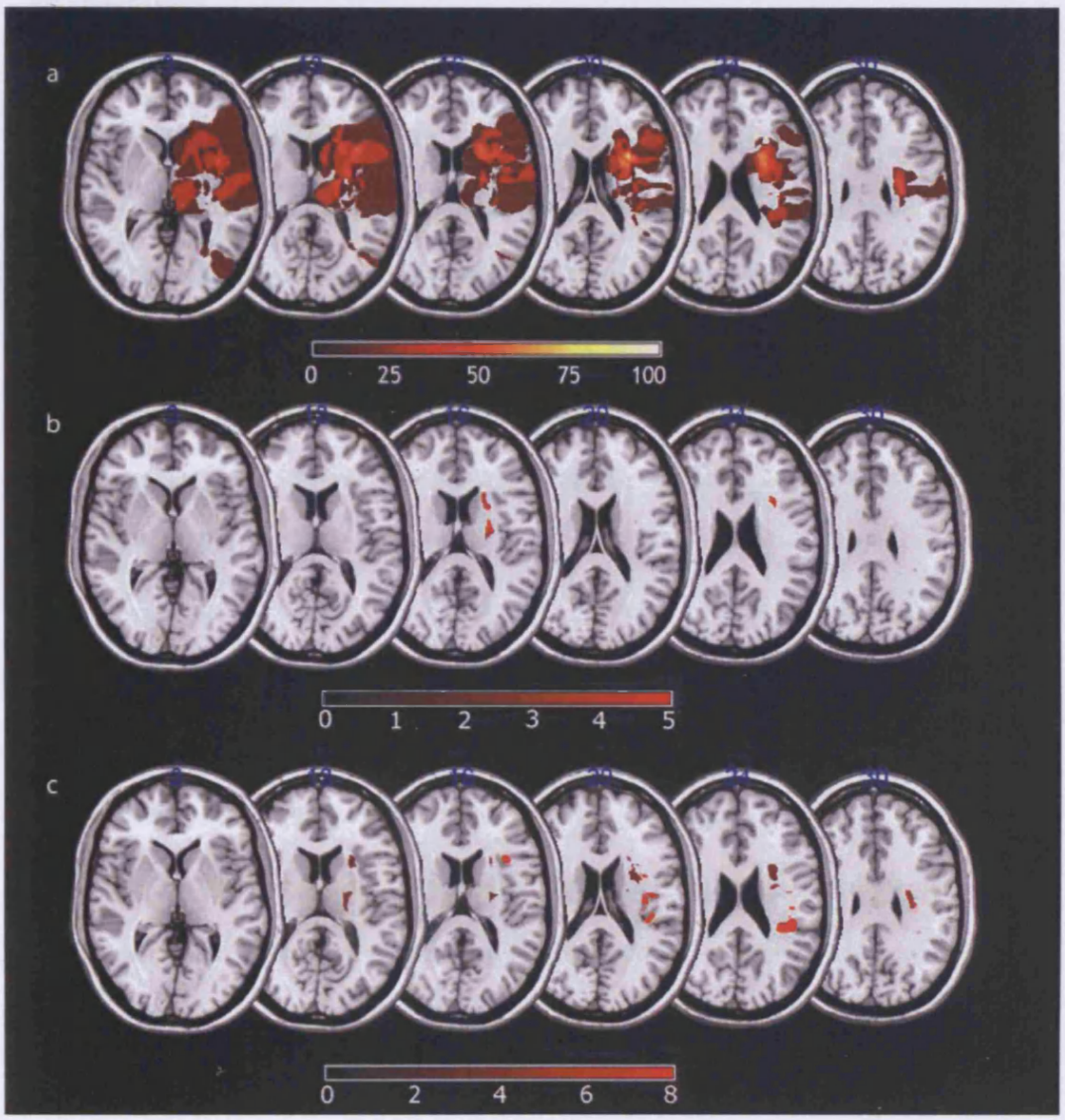


Figure 7.4 Lesion subtraction and Brunner Munzel statistic
Lesions were plotted using MRICro software (www.mricro.com) from either CT or MR. Lesion subtraction (patients with motor neglect minus those without) shows frontal white matter selectively affected in patients with motor neglect (a). (b) Brunner Munzel statistic revealed that right putamen and subcortical white matter were significantly associated (Z scores > 4.47) with abnormal performance in the masked prime task using the left, but not the right hand. (c) Severity of motor neglect is significantly associated (Z > 4.49) with damage at several discrete areas within the right hemisphere (including white matter near the putamen, inferior frontal gyrus, rolandic operculum and parietal supramarginal gyrus).

7.4 Discussion

This brief study reveals an impairment in the ability to inhibit ipsilesional limb motor plans in motor neglect. Specifically, patients with left motor neglect fail to inhibit partially activated right motor plans (evoked by the prime), which then intrude abnormally on left hand action planning, slowing down initiation of movement with the left hand. Our experimental finding correlated with the severity of motor neglect, suggesting that such a mechanism might be causative in the manifestation of motor neglect (Punt, Riddoch et al. 2005).

Consistent with our findings, one previous study revealed that monkeys with motor neglect following frontal lesions fail to inhibit their ipsilesional limb (Heilman, Valenstein et al. 1995). Such intrusion of rightward *incongruent* primes onto leftward movement occurs despite intact automatic inhibition of *congruent* primes following masked prime presentation, at least in some patients. We note also that asymmetries in performance on the masked prime task may be the result of asymmetric interactions between disrupted inhibition and response to target arrows, not simply inhibition failure alone (Sumner, Nachev et al. 2007).

Asymmetric intrusion of competing motor plans affecting left hand movements occurred particularly in patients with damage to the putamen and surrounding white matter, an area well connected to motor association and medial prefrontal regions. Interestingly, damage to the putamen has been associated with difficulty initiating movement in Parkinson's disease,

another condition where neglect-like phenomena occur in conjunction with inhibitory deficits (Playford, Jenkins et al. 1992; Ebersbach, Trottenberg et al. 1996). Dopaminergic therapy alleviates, to some extent, the inhibitory abnormalities found in patients with Parkinson's disease (Berardelli, Rona et al. 1996), raising the possibility of pharmacological intervention in motor neglect.

All patients also reported underutilisation of the contralesional limb. However, since there is no standard clinical test for motor neglect, we developed a severity score for motor neglect patients. This score reflects failure to move the contralesional limb during either bimanual or unimanual conditions, deficits sometimes referred to as motor extinction and motor impersistence respectively. The aim of the score was to provide an objective, simple bedside clinical test that might suggest the presence and severity of motor neglect. However, it should be noted that abnormal performance could result from other disorders, including unilateral Parkinson's disease, and so have to be interpreted appropriately in the clinical context.

When the severity score was compared to the lesion anatomy, several small motor association and subcortical brain regions significantly associated with increasing motor neglect severity were revealed, all consistent with previous anatomical descriptions of the condition (Laplane and Degos 1983; Triggs, Gold et al. 1994; von Giesen, Schlaug et al. 1994). TMS and PET activation studies also support the suggestion that while primary motor cortex tends to be intact in patients with motor neglect, it is damage to the motor association

areas that leads to the disorder (von Giesen, Schlaug et al. 1994; Classen, Schnitzler et al. 1997).

We propose that motor neglect results when breakdown in part of this motor association network, including the putamen, causes intrusion of right movement plans (due to failure of inhibition) onto left-sided action planning.

In summary, the findings reported in this chapter show that lateralized inhibitory deficits might be important in the genesis of motor neglect. We should highlight the fact that motor inhibition is likely to be a complex process involving interactions between multiple brain areas and we may have illuminated only one part of this network. Future work may investigate these complexities and in turn perhaps provide evidence for targeted therapeutic interventions to restore the inhibitory balance between the hemispheres such as TMS to the contralesional hemisphere, restraint therapy, used with some success in hemiparesis (Wolf, Winstein et al. 2006), or pharmacological intervention.

Chapter 8: General discussion

In this thesis I set out to explore the role of competition between motor programmes in action selection, and the contribution of the PPC to this process. Until recently, much of the focus of investigations into response competition or conflict has been on the role of frontal areas. However, as discussed in the Introduction, the PPC has both the connectivity and neuronal properties to be involved in response competition. For example, neurophysiological studies in monkeys have demonstrated activity within PPC related to response choice under situations of competition (Scherberger and Andersen 2007; Stoet and Snyder 2007). Moreover, a recent model has considered PPC, as well as premotor cortex, to be a key locus for the representation of conflicting action choices (Cisek 2007).

I considered the possibility that competing responses are propagated also in human PPC and that an imbalance in response competition may result in directional motor deficits in patients with neglect following posterior parietal damage. I tested the hypothesis that when there is competition between leftward and rightward response programmes, patients with right posterior parietal damage do not process leftward responses normally. Failure to represent competing leftward responses could result in the tendency of patients with right parietal damage to favour rightward movement. Such imbalance in resolving competition between response plans might contribute to the lateralised deficits found in the neglect syndrome.

8.1 Response competition in the human PPC

In order to investigate this hypothesis, patients with PPC damage and neglect were tested on a vertical variant of the Eriksen flanker task (Chapter 3). Subjects moved leftward or rightward as fast as possible using a small joystick according to a central target arrow. The target was flanked by arrows that were congruent (pointing in the same direction), incongruent (pointing in the opposite direction) or neutral (squares).

In stark contrast to normal subjects, patients with neglect following right PPC damage were actually faster to move rightward when the flanking arrows were leftward, i.e. in the right incongruent condition, than in the neutral condition **(Fig 3.3)**. In other words, they showed *facilitation* for rightward movements when flankers were incongruent. However, these patients had the expected *cost* of incongruence for *leftward* movements, similar in magnitude to the cost found bilaterally in normal subjects. Such a directional bias toward rightward movement implies that patients with PPC damage and neglect do not process leftward response plans (evoked by leftward flankers) in the same way as rightward ones. However, it is important to note that this lateralised abnormality occurred only when left and right response plans competed, i.e. in the incongruent condition. When there was no conflict between response plans (neutral and congruent conditions), leftward movements were as fast as rightward.

Next we considered whether this finding was specific to neglect patients with PPC damage. Facilitation for rightward incongruent movements did not

occur in a group of patients without significant PPC damage who also had neglect (**Fig 3.5**). In fact these patients were slower than patients with PPC damage in all conditions and had a disproportionately increased cost of incongruence *bilaterally*. Lesions for this non-PPC neglect group overlapped in inferior frontal white matter (**Fig 3.2**). Such susceptibility to incongruence was consistent with previous functional imaging work which has suggested that frontal regions may be important for reducing delays due to flanker interference by mediating 'cognitive control' (MacDonald, Cohen et al. 2000).

Two further control groups – patients with right hemisphere damage without neglect and those with left PPC damage – had normal incongruence costs, both leftward and rightward. There were no patients with PPC damage in the group of patients without neglect as it is our experience that the vast majority of patients with PPC damage have neglect if tested early enough (Mort, Malhotra et al. 2003). Therefore, this first experiment supports a specific role for the *right* PPC in propagation of leftward flanker-induced competing response programs.

A subsidiary analysis of the flanker data was performed to investigate directional slowing in patients with neglect (**Fig 3.6**). Previous work on patients with neglect following right hemisphere stroke revealed a tendency to initiate leftward movements more slowly than rightward – leftward directional hypokinesia (DH) (Mattingley, Bradshaw et al. 1992; Behrmann and Meegan 1998; Mattingley, Husain et al. 1998; Husain, Mattingley et al.

2000). Mattingley and colleagues suggest that leftward DH resulted from a motor deficit in planning leftward action in patients with right PPC damage, whereas patients with frontal damage had a spatial visuomotor deficit for objects on the left side of space (**Fig 1.6**) (Mattingley, Husain et al. 1998; Husain, Mattingley et al. 2000).

We found patients with PPC neglect were slower to move leftward than rightward only in the incongruent condition, whereas patients with right insular damage were slower to move left than right selectively in the neutral condition. Therefore two forms of directional hypokinesia occur in patients with neglect. Patients with PPC damage and neglect have relative leftward slowing only when response plans compete – in the incongruent condition. This reflects failure to propagate competing *leftward* response plans in the right incongruent condition, thus making this condition significantly faster than the leftward incongruent condition. In contrast, when neglect is the result of anterior damage, directional hypokinesia occurs perhaps because patients are more distracted by the "pop-out" effect of neutral squares when planning leftward movements. Thus patients with frontal damage are susceptible to visual distraction while planning leftward movement. In support of this, a further experiment in normal subjects confirmed that the neutral squares did cause delay compared with a no flanker condition.

8.2 Directional masked primes

Next, we investigated whether such a deficit in processing competing leftward motor programs occurs when masked (invisible) primes, rather than

flankers, induce the competing response plans (Chapter 4). In the masked prime paradigm, the primes are not visually perceived (Eimer and Schlaghecken 1998; Eimer 1999). Despite this, masked primes still affect the speed of reaction to a subsequent target arrow (Eimer and Schlaghecken 1998; Eimer 1999; Sumner, Nachev et al. 2007). All previous studies of masked primes have investigated the relative effects of incongruent verses congruent primes (Schlaghecken and Eimer 1997; Eimer and Schlaghecken 1998; Eimer 1999; Seiss and Praamstra 2004; Seiss and Praamstra 2006; Sumner and Husain 2007; Sumner, Nachev et al. 2007; Sumner 2008). However, in this chapter we investigate the magnitude of the effect of *leftward* compared with *rightward* primes.

In patients with right hemisphere stroke, unlike normal controls, the effect of the left prime was significantly less than that of the right across both movement directions (**Fig 4.3**). However, there was variability within the patient group. Using the Brunner Munzel rank order statistic, we showed that patients who processed the left prime least had right PPC damage (**Fig 4.4**). Therefore, in this second paradigm PPC damage was again associated with failure to propagate competing leftward response programs.

Taken together, data from both Chapters 3 and 4 suggest that patients with PPC damage manifest a directional imbalance whereby leftward action plans are not activated as strongly as rightward action plans, particularly when there is competition between responses. However in both these paradigms decoding of an arrow stimulus is required. Even though the masked prime

arrows are not visually perceived, the fact that leftward and rightward prime arrows differentially affect movement speeds suggests that prime arrows undergo some level of signal-response transformation. Therefore, it is possible that patients with PPC damage have a directional deficit at the level of stimulus decoding, that is, they fail to decode leftward, but not rightward response stimuli when the two are visually activated (Bunge, Hazeltine et al. 2002; Cavina-Pratesi, Valyear et al. 2006). In the next chapter we probed further whether patients with PPC damage have a deficit at the level of signal response transformations only, or whether they could be considered to have a true directional motor deficit.

8.3 Free choice and response competition

In the free choice paradigm employed in Chapter 5, subjects had to choose to move leftward or rightward as quickly as possible when two, vertically aligned squares were presented. Since, there was no directional visual information to guide subjects' choice, rightward and leftward response plans can be considered to compete maximally with one another and the decision to move leftward or rightward is the result of this competition. Both Brunner Munzel analysis and more conventional statistics, where patients are divided in advance according to lesion site, suggested that right PPC damage was associated with the tendency to choose to move right rather than left (**Fig 5.5**). Therefore even without visual signals that required decoding, patients with PPC damage appear to have a motoric rightward bias such that leftward response plans do not compete equally with rightward.

Can this rightward bias be influenced by masked primes? Previous work has shown a negative compatibility effect on response choice using masked primes (Schlaghecken and Eimer 2004). This was replicated in normal subjects in the second free choice paradigm in **Chapter 5**. In contrast patients with PPC damage showed the opposite pattern of performance, tending to make more rightward choices following a rightward prime. While this could be consistent with failure of patients with right PPC damage to inhibit the motor programs activated by a rightward prime, there was considerable variability between patients in overall response bias and further work examining patients with and without PPC lesions would be required to illuminate this further.

8.4 Asymmetries in normal individuals during response conflict

Chapter 6 reports investigations concerning asymmetries in response conflict in normal subjects. Although the main focus of this thesis is to investigate the effects of right hemisphere damage on motor processing, the results of the Eriksen flanker task used in Chapter 3 suggested that normal subjects had greater incongruence costs for leftward than rightward movements. Therefore we asked whether leftward and rightward competing responses are processed differentially in normal subjects.

Again we used a variation of the Eriksen flanker task, but this time the proportion of movements in each direction was varied – movement proportions across three sessions were 50% in either direction, or 80% leftward, or 80% rightward. In other words, in one session, there were equal

proportions of rightward and leftward movements, while in two other sessions 80% of responses was either rightward or leftward. When 80% of movements were in one direction or the other, the incongruence cost was greater in the *more frequent* direction. This imbalance can be explained by the relative novelty of leftward flankers, say, when 80% of movements were rightward, thereby leading to greater slowing when such *leftward* incongruent flankers were present. The converse of a novelty effect is the adaptation demonstrated in the frequently moved direction, i.e. attenuation of the effect of the very commonly presented stimulus (*rightward* in this example). Such adaptation could occur either at the level of stimulus presentation or motor programming or both.

Importantly, the relative adaptation in the frequently moved direction was asymmetric. We found that the incongruence reaction time was greater for leftward movements (with rightward flankers) when 80% of movements were rightward, than in the rightward direction (with leftward flankers) when 80% of movements were left (**Fig 6.1**). Therefore, there is greater adaptation and consequent attenuation of the effect of leftward arrows than rightward in normal individuals.

How can this be explained? One possibility is that at some stage there are completely different processing streams for the two directions, although, both would have to lead to a common output pathway. Alternatively, perhaps there are bilateral representations of rightward, but not leftward response

plans (so it is easier to reduce the effect of left flankers by adaptation because they are processed in only one rather than two locations).

This latter explanation could explain why there were no response competition deficits found after left PPC damage in the Eriksen flanker task (Chapter 3). If right PPC neurons represent both leftward and rightward response plans whereas left PPC has only rightward representations, right PPC would be able to compensate for left PPC damage to some extent. Such a proposal is analogous to the argument that spatial neglect is particularly prominent following right hemisphere stroke because the right hemisphere is dominant for spatial representation and covers both the right and left sides of space, whereas, the left hemisphere only mediates spatial attention toward the right (Mesulam 1981; Mesulam 1999).

8.5 Motor neglect

The final experimental chapter investigated motor neglect, where patients fail to use their contralesional limb, despite normal power and sensation. Although many patients with motor neglect will also have spatial neglect and hemiparesis, we were able to study some patients *without* significant hemiparesis who had motor neglect and varying degrees of spatial neglect. Seven patients with motor neglect and six without performed a masked prime task using left and right hands (signalled by left and right arrows respectively). When masked prime and target are separated by 200ms, normal subjects are slower to move in response to the target arrow when the prime and target point in the same direction (Sumner, Nachev et al. 2007). This is known as the negative compatibility effect.

In contrast to this, neither right-hemisphere patient group had a negative compatibility effect. There was a distinct pattern of performance found in the patients with motor neglect only (**Fig 7.1**). These individuals were particularly slow when a right prime preceded a left hand movement suggesting that they were susceptible to interference from right arm response programs when planning leftward movements. This perhaps helps to explain why they favour use of the right over the left arm. Such an asymmetric deficit in the motor neglect patients was particularly associated with lesions within the putamen, perhaps implicating the region as an important node within the network for bimanual motor planning.

8.6 Conclusions

The first conclusion reached is that PPC in humans does have a role in propagation of leftward motor programs for the right arm, most evident when there is competition between motor programs. In other words, people with right PPC damage are able to move their right arms in either direction, but under situations of response conflict rightward responses are favoured over leftward movements. The first evidence for this emerged in the conflict experiment of Chapter 3 when a selective deficit for processing competing *leftward* motor programs occurred in patients with right PPC damage. The findings reported in Chapters 4 and 5 suggest that even when the competing motor programs were not visually perceived (masked primes) or entirely self-generated (free choice), such patients still favoured rightward over leftward motor programs.

Throughout this thesis, I also sought to investigate whether or not right PPC truly had a motoric role in addition to the well described sensory and attentional functions (Gottlieb, Kusunoki et al. 1998; Cavina-Pratesi, Valyear et al. 2006; Goldberg, Bisley et al. 2006). Perhaps the most compelling evidence of a motor role for PPC comes from the free choice paradigm (Chapter 5), where choice was made between leftward and rightward action without visual stimuli to suggest the direction. Patients with right PPC damage still chose right more often than left implicating PPC in programming the directional response choices. Such data suggest that PPC is involved in motor planning, but this is not to say that the role of PPC is purely motoric. Clear cut sensory and attentional PPC functions have, of course, previously been shown (Corbetta 1998; Corbetta and Shulman 2002). It is possible that specific sub-regions within the human PPC are more involved in the motoric processes considered here. However, the resolution and limitations of lesion mapping do not permit a great deal of speculation on this count (for further discussion see Husain and Nachev 2007).

How does PPC process motor information? Patients with PPC damage fail to process directional information particularly when there is competition between action choices. In the incongruent condition of the directional flanker task (Chapter 3), patients with right PPC damage lost the normal incongruence cost for rightward movements (with leftward flankers). Therefore it appears that activation of response choices within PPC normally leads to a delay in response. We propose that multiple response alternatives

may be activated within PPC and mutually inhibit one another, thereby slowing propagation through the motor control system. But what is the point of such a delay?

Most discussions of the incongruence 'cost' (reaction time delay) observed in the Eriksen flanker task consider it to be a feature that should optimally be suppressed if subjects are to make rapid responses. In predictable circumstances, simple 'rules' might be applied at early stages of processing to eliminate the effect of competing responses between the central target cue and peripheral, irrelevant flankers. However, although the cost evoked by flankers is modifiable it is never to our knowledge completely eliminated, suggesting competition is a robust process or even perhaps hardwired to occur within our nervous systems.

Movement delay, therefore, is the result of competition between alternative responses. But rather than considering this simply as an inevitable cost, the delay evoked by conflict might actually also be functionally important, allowing selection between competing action choices before the response is made. For an animal, it might be worth paying the penalty of a small increase in reaction time (evoked by such conflict) to ensure that the most appropriate response is made. Even if some potential action choices are often irrelevant, there may be occasions when they represent the best response particularly in natural, unpredictable environments. For example, a sudden change in the luminance of the visual scene may require very different responses depending upon the cause: if it is simply due to shadows cast by clouds we

may be able to ignore this and continue with the task at hand, but if it is due to falling masonry or bricks we need to take aversive action rapidly. Here two action plans are potentially in conflict and the brain has to make a decision, based on prior probabilities and accumulating evidence, on which to select. Thus although the competition evoked by flanker stimuli in the Eriksen paradigm are always irrelevant, this would not invariably be the case for stimuli in the real world.

According to this view, therefore, both relevant and irrelevant competing stimulus-response association signals propagate in the brain, mutually inhibiting each other and leading to a reaction time delay. Indeed, many current decision-making models of response choice involve accumulation of evidence, in distributed brain regions, for each competing choice until decision thresholds are reached (Cisek and Kalaska 2002; Glimcher 2003; Smith and Ratcliff 2004; Cisek and Kalaska 2005; Rorie and Newsome 2005; Cisek 2006; Cisek 2007). From this perspective, *competition* between conflicting responses is a crucial process for action selection, analogous to models that propose competition to be a key part of selection for sensory attention (Desimone and Duncan 1995; Duncan, Humphreys et al. 1997). Of course, the eventual response is likely to be based on the outcome of competition *biased* by many different aspects of an animal's state (e.g., previous experience, reward contingencies, and task-set) as well as changes in the environment (e.g., new information that alters the weight given to a particular stimulus).

While the data in this thesis do not directly investigate this issue, it is possible that propagation and inhibition of response programs within parietal lobe are also biased by other spatial or sensory characteristics of the stimulus activating the response or contextual stimuli. An example of this would be that perhaps objects with novel features would be propagated more strongly and lead to greater inhibition of competing potential responses. Therefore response programming could be constantly updated according to the sensory environment.

How does activity within PPC interact with motor processing known to occur within other more anterior brain areas? Evidence from Chapter 3 suggests that visuomotor signals are processed in at least two partially *independent* streams: one inactivated by damage to inferior frontal white matter and the other requiring intact right PPC. Patients with damage in the more anterior stream, were generally slow to respond and were disproportionately distracted by conflicting information. In contrast to the patients with parietal damage who, as discussed above, failed to process competing leftward motor programs and were consequently much less susceptible to distracting leftward information when planning right movements.

The schematic shown in **Figure 8.1** illustrates how parietal and prefrontal processing streams may interact based on the findings presented in Chapter 3. Neurophysiological studies in monkeys have suggested that multiple programming streams may converge in premotor cortex where the action

signal is consolidated leading to a motor response (Cisek and Kalaska 2002; Cisek and Kalaska 2005; Cisek 2006; Cisek 2007). The graphs on the right hand of **Figure 8.1** are simplistic representations of activity in premotor cortex. The assumption is that when neural activity passes a threshold, a response will occur.

When there is no conflict (a), the stimulus leads to a response of a given latency. However, when conflict occurs, both competing responses (left and right) will propagate within PPC and mutual inhibition between them will lead to a delay in output (red line on graph). In contrast, prefrontal regions act to boost the target response and speed output, perhaps by inhibiting flanker responses due to their location – so-called 'cognitive control' in current parlance (Botvinick, Nystrom et al. 1999; Botvinick, Braver et al. 2001; Botvinick, Cohen et al. 2004; Ullsperger, Bylsma et al. 2005). The net result of these two subsystems is the small delay in response that occurs in normal individuals.

When the PPC is damaged, no delay ensues, but the independent, intact prefrontal system still boosts and consequently speeds the response (c). This would explain the facilitation (below the neutral baseline) we observed in patients with PPC damage. If right PPC damage leads to selective loss of leftward motor programs, then facilitation would occur for the right incongruent condition only. In contrast, when prefrontal regions are damaged, the delay is longer (d), as it was in the patients with more anterior damage in Chapter 3. This delay was bilateral perhaps because prefrontal regions have a

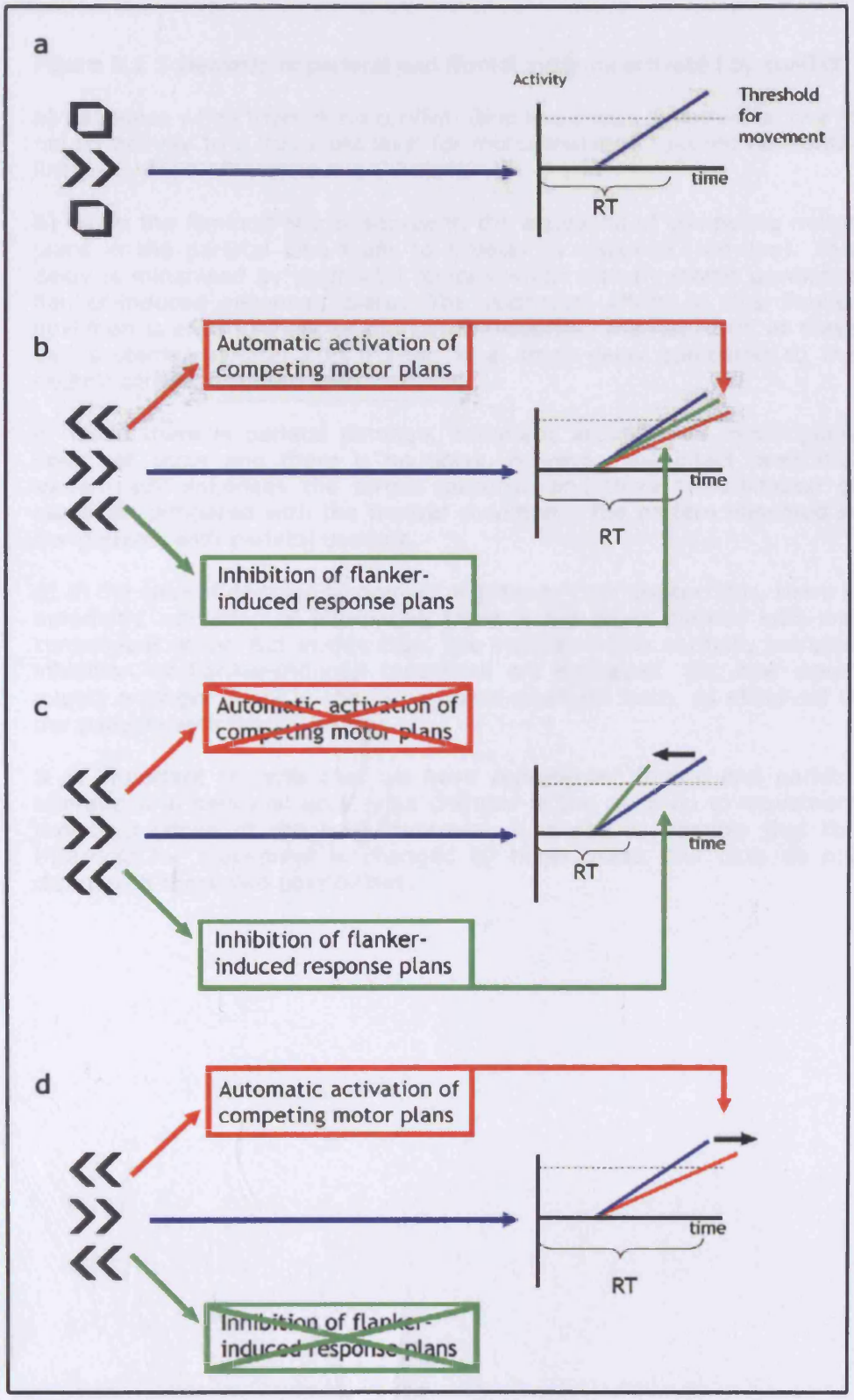

a
Activity
Threshold for movement
time
RT
b
Automatic activation of competing motor plans
time
RT
Inhibition of flanker-induced response plans
c
Automatic activation of competing motor plans
time
RT
Inhibition of flanker-induced response plans
d
Automatic activation of competing motor plans
time
RT
Inhibition of flanker-induced response plans

Figure 8.1 Schematic of parietal and frontal systems activated by conflict

a) Response when there is no conflict. Blue line shows hypothetical rise in neural activity to a threshold level for motor initiation (dashed horizontal line)

b) When the flankers are incongruent, the activation of competing motor plans in the parietal lobe leads to a delay in response (red line). This delay is minimised by prefrontal regions which actively inhibit unwanted flanker-induced response plans. The reciprocal effect of this flanker inhibition is enhancement of the target response. The net result of these two systems, parietal and frontal, is a small delay compared to the neutral condition (green line).

c) When there is parietal damage, automatic activation of motor plans does not occur and there is no delay. However, the intact prefrontal system still enhances the target response and there is facilitation of response compared with the neutral condition – the pattern observed in our patients with parietal damage.

d) In the case of damage to prefrontal areas or their connections, there is automatic activation of alternative plans in the intact parietal lobe and consequent delay. But in this case, the systems which normally increase inhibition of flanker-induced responses are damaged. So, one would expect a longer delay in the incongruent condition such, as observed in our patients with frontal lesions.

It is important to note that we have represented frontal and parietal alterations in neuronal activity as changes in the ramp up to movement threshold (slope of the line). However, it is equally possible that the threshold for movement is changed by these areas. Our data do not distinguish these two possibilities.

bilateral (although possibly asymmetric) role in reducing susceptibility to interference.

Prefrontal regions, particular the anterior cingulate, have previously been proposed to detect conflict and recruit other areas such as dorsolateral prefrontal cortex to minimise intrusion from conflicting information (Botvinick, Nystrom et al. 1999; Botvinick, Braver et al. 2001; Botvinick, Cohen et al. 2004; Ullsperger, Bylsma et al. 2005). While this interpretation would be consistent with our schematic, there is no need to invoke a generic "conflict detector" to explain our data. Conflict-induced "boosting", proposed to occur in anterior brain regions, could result from application of a simple, task-specific rule (e.g "inhibit directional stimuli at flanker locations"), assuming that inhibition of leftward arrows results in facilitation of the alternative, rightward direction and vice versa (Eimer 1999).

One important finding was that we did not find comparable effects after left PPC damage. It is possible that normally the left PPC is involved in propagating rightward responses, just as the right PPC plays a role in activating leftward responses. However, following left PPC damage we did not observe any facilitation for leftward responses when leftward targets were accompanied by rightward flankers. Thus, we have to conclude that the right PPC and/or other regions can compensate for left PPC damage and still represent rightward responses. Further studies will be required to examine this issue in more detail but clinical observations have demonstrated for many years that while neglect is more common and prominent after right

PPC damage, limb apraxia is far more frequent after left PPC damage. How these findings relate to this asymmetry in clinical syndromes following PPC damage remains a (formidable) challenge for future investigations.

Does the right PPC perform a role in response competition regardless of whether responses are self-generated or instructed? Patients with PPC damage tended to choose to move right more often than left even when given a free choice (Chapter 5), consistent with failure to propagate leftward response plans even when they are freely chosen. However, there was variability between patients and the patients with PPC damage made only a few more rightward than leftward movements. Therefore it is likely that several factors, such as strategic advanced planning of response direction or covert attentional asymmetries – as well as a competitive bias to the right – may influence response choice.

Comparison of two masked prime experiments did hint at the fact that freely *choosing* action may involve different parietal mechanisms from those involved in resolving competition between *instructed* actions (Chapter 4 and Chapter 5, experiment 2). The influence of masked primes on response choice in five patients with right PPC damage was remarkably consistent – in that patients went right more often after a right than a left prime – and opposite to that of normal subjects (although the degree of overall rightward bias varied within the patient group). However, these patients did not perform similarly when the responses were *instructed* in Chapter 4, despite all having PPC damage. Although patient numbers are too small to make

firm inference from this finding, it suggests perhaps that different mechanisms or subdivisions of PPC are involved in resolving competition for freely chosen versus instructed action.

In conclusion, the data presented above have suggested that right PPC is important for normal processing of directional motor programs. Patients with right PPC damage may not propagate competing leftward motor programs and this in turn may lead to disinhibition of rightward motor programs resulting effectively in a tendency to be over impulsive towards the right. Such imbalance could contribute to neglect behaviour. Multiple processing streams exist for visuomotor processing, and channels within the human PPC appear to be independent from those within more anterior regions of brain. Independent processing streams may converge on a critical node in premotor cortex and influence response choice and speed. Several unanswered questions remain, including the way in which response competition between action plans may be biased within PPC perhaps by sensory stimuli or even task goals. However, the findings presented here provide a platform to investigate these issues and the asymmetry of PPC function in humans further.

References

Andersen, R. A. (1995). "Encoding of Intention and Spatial Location in the Posterior Parietal Cortex." Cerebral Cortex **5**(5): 457-469.

Andersen, R. A. (1997). "Multimodal integration for the representation of space in the posterior parietal cortex." Philosophical Transactions of The Royal Society Lond B **1997**(352): 1421-1428.

Andersen, R. A. and C. A. Buneo (2002). "Intentional maps in posterior parietal cortex." Annu Rev Neurosci **25**: 189-220.

Aron, A. R., P. C. Fletcher, et al. (2003). "Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans (vol 6, pg 115, 2003)." Nature Neuroscience **6**(12): 1329-1329.

Aron, A. R., T. W. Robbins, et al. (2004). "Inhibition and the right inferior frontal cortex." Trends Cogn Sci **8**(4): 170-7.

Bartolomeo, P., S. Chokron, et al. (2001). "Laterally directed arm movements and right unilateral neglect after left hemisphere damage." Neuropsychologia **39**(10): 1013-1021.

Bartolomeo, P., P. D'Erme, et al. (1998). "Perception and action in hemispatial neglect." Neuropsychologia **36**(3): 227-237.

Bartolomeo, P., M. Thiebaut de Schotten, et al. (2007). "Left unilateral neglect as a disconnection syndrome." Cereb Cortex **17**(11): 2479-2490.

Batista, A. P., C. A. Buneo, et al. (1999). "Reach plans in eye-centred coordinates." Science **285**: 257-260.

Battaglia-Mayer, A., R. Caminiti, et al. (2003). "Multiple Levels of Representation of Reaching in the Parieto-frontal Network." Cereb. Cortex **13**(10): 1009-1022.

Behrmann, M., T. Ghiselli-Crippa, et al. (2001). "Impaired initiation but not execution of contralesional saccades in hemispatial neglect." Behav Neurol **13**(1,2): 39-60.

Behrmann, M. and D. V. Meegan (1998). "Visuomotor processing in unilateral neglect." Conscious Cogn **7**(3): 381-409.

Berardelli, A., S. Rona, et al. (1996). "Cortical inhibition in Parkinson's disease: A study with paired magnetic stimulation." Brain **119**(1): 71-77.

Bisiach, E., G. Geminiani, et al. (1990). "Perceptual and premotor factors of unilateral neglect." Neurology **40**(8): 1278-81.

Bisiach, E. and C. Luzzatti (1978). "Unilateral neglect of representational space." Cortex **14**: 129-133.

Bisiach, E., R. Ricci, et al. (1998). "Perceptual and response bias in unilateral neglect: Two modified versions of the Milner Landmark task." Brain and Cognition **37**(3): 369-386.

Bisley, J. W. and M. E. Goldberg (2003). "Neuronal activity in the lateral intraparietal area and spatial attention." Science **299**(5603): 81-6.

Blank, S. C., S. K. Scott, et al. (2002). "Speech production: Wernicke, Broca and beyond." Brain **125**(8): 1829-1838.

Blasi, G., T. E. Goldberg, et al. (2006). "Brain regions underlying response inhibition and interference monitoring and suppression." European Journal of Neuroscience **23**(6): 1658-1664.

Botvinick, M., D. J. Cohen, et al. (2004). "Conflict monitoring and anterior cingulate cortex: an update." Trends Cogn Sci **8**(12): 539-546.

Botvinick, M., L. E. Nystrom, et al. (1999). "Conflict monitoring versus selection-for-action in anterior cingulate cortex." Nature **402**: 179-181.

Botvinick, M. M., T. S. Braver, et al. (2001). "Conflict monitoring and cognitive control." Psychol Rev **108**(3): 624-52.
Botvinick, M. M., T. S. Braver, et al. (2001). "Conflict monitoring and cognitive control." Psychological Review **108**(3): 624-652.
Bracewell, R. M., P. Mazzoni, et al. (1996). "Motor intention activity in the macaque's lateral intraparietal area. II. Changes of motor plan." J Neurophysiol **76**(3): 1457-64.
Brain, R. W. (1941). "Visual disorientation with special reference to lesions of the right cerebral hemisphere." Brain **64**: 244-272.
Brass, M. and P. Haggard (2007). "To do or not to do: The neural signature of self-control." Journal of Neuroscience **27**(34): 9141-9145.
Braver, T. S., D. M. Barch, et al. (2001). "Anterior cingulate cortex and response conflict: effects of frequency, inhibition and errors." Cereb Cortex **11**(9): 825-36.
Buneo, C. A. and R. A. Andersen (2006). "The posterior parietal cortex: Sensorimotor interface for the planning and online control of visually guided movements." Neuropsychologia **44**(13): 2594-2606.
Buneo, C. A., M. R. Jarvis, et al. (2002). "Direct visuomotor transformations for reaching." Nature **416**(6881): 632-6.
Bunge, S. A., E. Hazeltine, et al. (2002). "Dissociable contributions of prefrontal and parietal cortices to response selection." Neuroimage **17**(3): 1562-1571.
Buxbaum, L. J., M. K. Ferraro, et al. (2004). "Hemispatial neglect: Subtypes, neuroanatomy, and disability." Neurology **62**(5): 749-56.
Buxbaum, L. J., K. M. Kyle, et al. (2006). "Neural substrates of knowledge of hand postures for object grasping and functional object use: Evidence from fMRI." Brain Research **1117**: 175-185.
Carter, C., V. Van Veen, et al. (2001). "Conflict and the evaluative functions of the anterior cingulate: Converging evidence from event-related fMRI and high density ERP." Neuroimage **13**(6): S305-S305.
Carter, C. S., M. M. Botvinick, et al. (1999). "The contribution of the anterior cingulate cortex to executive processes in cognition." Reviews in the Neurosciences **10**(1): 49-57.
Carter, C. S., T. S. Braver, et al. (1998). "Anterior cingulate cortex, error detection, and the online monitoring of performance." Science **280**(5364): 747-9.
Casey, B. J., K. M. Thomas, et al. (2000). "Dissociation of response conflict, attentional selection, and expectancy with functional magnetic resonance imaging." Proceedings of the National Academy of Sciences of the United States of America **97**(15): 8728-8733.
Cavina-Pratesi, C., K. F. Valyear, et al. (2006). "Dissociating arbitrary stimulus-response mapping from movement planning during preparatory period: Evidence from event-related functional magnetic resonance imaging." Journal of Neuroscience **26**(10): 2704-2713.
Chieffi, S., M. Gentilucci, et al. (1993). "Study of Selective Reaching and Grasping in a Patient with Unilateral Parietal Lesion - Dissociated Effects of Residual Spatial Neglect." Brain **116**: 1119-1137.
Cisek, P. (2006). "Integrated neural processes for defining potential actions and deciding between them: a computational model." J Neurosci **26**(38): 9761-9770.

Cisek, P. (2007). "Cortical mechanisms of action selection: the affordance competition hypothesis." Philos Trans R Soc Lond B Biol Sci **362**(1485): 1585-1599.
Cisek, P. and J. Kalaska (2002). "Simultaneous encoding of multiple potential reach directions in dorsal premotor cortex." Journal of Neurophysiology **87**: 1149-1154.
Cisek, P. and J. Kalaska (2005). "Neural correlates of reaching decisions in dorsal premotor cortex: specification of multiple direction choices and final selection of action." Neuron **45**: 801-814.
Classen, J., A. Schnitzler, et al. (1997). "The motor syndrome associated with exaggerated inhibition within the primary motor cortex of patients with hemiparetic." Brain **120**(4): 605-619.
Cocchini, G., N. Beschin, et al. (2001). "The fluff test: a simple task to assess body representation neglect." Neuropsychological Rehabilitation **11**: 17-31.
Cohen, A., R. Irvy, et al. (1995). "Response code activation by signals in the neglected hemifield." Neuropsychology **9**: 165-173.
Colby, C. and M. E. Goldberg (1999). "Space and attention in parietal cortex." Annual Review of Neuroscience **22**: 319-49.
Colby, C. L. (1998). "Action-oriented spatial reference frames in cortex." Neuron **20**(1): 15-24.
Colby, C. L. and J. R. Duhamel (1996). "Spatial representations for action in parietal cortex." Cognitive Brain Research **5**(1-2): 105-115.
Connolly, J. D., R. A. Andersen, et al. (2003). "FMRI evidence for a 'parietal reach region' in the human brain." Exp Brain Res **153**(2): 140-5.
Constantinidis, C. and M. A. Steinmetz (2001). "Neuronal responses in area 7a to multiple-stimulus displays: I. neurons encode the location of the salient stimulus." Cerebral Cortex **11**: 581-591.
Corbetta, M. (1998). "Frontoparietal cortical networks for directing attention and the eye to visual locations: identical, independent, or overlapping neural systems?" Proc Natl Acad Sci U S A **95**(3): 831-8.
Corbetta, M. and G. L. Shulman (2002). "Control of goal-directed and stimulus-driven attention in the brain." Nature Reviews Neuroscience **3**: 215-229.
Coslett, H. B., D. Bowers, et al. (1990). "Directional Hypokinesia and Hemispatial Inattention in Neglect." Brain **113**: 475-486.
Coulthard, E., A. Parton, et al. (2006). "Action control in visual neglect." Neuropsychologia **44**(13): 2717-2733.
Coulthard, E., A. Parton, et al. (2007). "The modular architecture of the neglect syndrome: Implications for action control in visual neglect." Neuropsychologia **45**(8): 1982-1984.
Critchley, H. D., C. J. Mathias, et al. (2003). "Human cingulate cortex and autonomic control: converging neuroimaging and clinical evidence." Brain **126**(10): 2139-2152.
Cui, H. and R. A. Andersen (2007). "Posterior Parietal Cortex Encodes Autonomously Selected Motor Plans." Neuron **56**(3): 552-559.
Culham, J. C., S. L. Danckert, et al. (2003). "Visually guided grasping produces fMRI activation in dorsal but not ventral stream brain areas." Experimental Brain Research **153**(2): 180-189.
de Jong, B. M. and A. M. J. Paans (2007). "Medial versus lateral prefrontal dissociation in movement selection and inhibitory control." Brain Research **1132**(1): 139-147.

De Renzi, E. (1982). Disorders of space exploration and cognition. New York, Wiley.
Desimone, R. and J. Duncan (1995). "Neural mechanisms of selective visual attention." Annual Review of Neuroscience **18**: 193-222.
Desmurget, M., C. M. Epstein, et al. (1999). "Role of the posterior parietal cortex in updating reaching movements to a visual target." Nature Neuroscience **2**(6): 563-567.
Desmurget, M. and S. Grafton (2000). "Forward modeling allows feedback control for fast reaching movements." Trends in Cognitive Sciences **4**(11): 423-431.
Doricchi, F. and F. Tomaiuolo (2003). "The anatomy of neglect without hemianopia: a key role for parietal-frontal disconnection?" Neuroreport **14**(17): 2239-43.
Driver, J. and J. B. Mattingley (1998). "Parietal neglect and visual awareness." Nat Neurosci **1**(1): 17-22.
Duhamel, J. R., F. Bremmer, et al. (1997). "Spatial invariance of visual receptive fields in parietal cortex neurons." Nature **389**(6653): 845-848.
Duhamel, J. R., C. L. Colby, et al. (1992). "The Updating of the Representation of Visual Space in Parietal Cortex by Intended Eye-Movements." Science **255**(5040): 90-92.
Duncan, J., G. Humphreys, et al. (1997). "Competitive brain activity in visual attention." Current Opinion in Neurobiology **7**: 255-261.
Duncan, J. and A. M. Owen (2000). "Common regions of the human frontal lobe recruited by diverse cognitive demands." Trends in Neurosciences **23**(10): 475-483.
Durston, S., M. C. Davidson, et al. (2003). "Parametric manipulation of conflict and response competition using rapid mixed-trial event-related fMRI." Neuroimage **20**(4): 2135-2141.
Ebersbach, G., T. Trottenberg, et al. (1996). "Directional bias of initial visual exploration A symptom of neglect in Parkinson's disease." Brain **119**(1): 79-87.
Egner, T. and J. Hirsch (2005). "Cognitive control mechanisms resolve conflict through cortical amplification of task-relevant information." Nature Neuroscience **8**(12): 1784-1790.
Egner, T. and J. Hirsch (2005). "The neural correlates and functional integration of cognitive control in a Stroop task." NeuroImage **24**(2): 539-547.
Eimer, M. (1999). "Facilitatory and inhibitory effects of masked prime stimuli on motor activation and behavioural performance." Acta Psychologica **101**(2-3): 293-313.
Eimer, M. and F. Schlaghecken (1998). "Effects of masked stimuli on motor activation: Behavioral and electrophysiological evidence." Journal of Experimental Psychology-Human Perception and Performance **24**(6): 1737-1747.
Eimer, M. and F. Schlaghecken (2001). "Response facilitation and inhibition in manual, vocal, and oculomotor performance: Evidence for a modality-unspecific mechanism." Journal of Motor Behavior **33**(1): 16-26.
Eimer, M., A. Schubo, et al. (2002). "Locus of inhibition in the masked priming of response alternatives." Journal of Motor Behavior **34**(1): 3-10.
Elsinger, C. L., D. L. Harrington, et al. (2006). "From preparation to online control: Reappraisal of neural circuitry mediating internally generated and externally guided actions." Neuroimage **31**(3): 1177-1187.

Eriksen, B. A. and C. W. Eriksen (1974). "Effects of Noise Letters Upon Identification of a Target Letter in a Nonsearch Task." Perception & Psychophysics **16**(1): 143-149.
Eriksen, C. W. (1995). "The flankers task and response competition: a useful tool for investigating a variety of cognitive problems." Visual Cognition **2**(2/3): 101-118.
Faugier-Grimaud, S., C. Frenois, et al. (1985). "Effects of posterior parietal lesions on visually guided movements in monkeys." Exp Brain Res **59**(1): 125-38.
Faugier-Grimaud, S., C. Frenois, et al. (1978). "Effects of posterior parietal lesions on visually guided behavior in monkeys." Neuropsychologia **16**(2): 151-68.
Fellows, L. K. and M. J. Farah (2005). "Is anterior cingulate cortex necessary for cognitive control?" Brain **128**: 788-796.
Ferber, S. and J. Danckert (2006). "Lost in space--The fate of memory representations for non-neglected stimuli." Neuropsychologia **44**(2): 320-325.
Ferber, S. and H. Karnath (2001). "How to assess spatial neglect - line bisection or cancellation tasks?" Journal of Clinical and Experimental Neuropsychology **23**: 599-607.
Ferber, S. and H. O. Karnath (2001). "How to assess spatial neglect--line bisection or cancellation tasks?" J Clin Exp Neuropsychol **23**(5): 599-607.
Fisk, J. D. and M. A. Goodale (1988). "The Effects of Unilateral Brain-Damage on Visually Guided Reaching - Hemispheric-Differences in the Nature of the Deficit." Experimental Brain Research **72**(2): 425-435.
Frith, C. D., K. Friston, et al. (1991). "Willed Action and the Prefrontal Cortex in Man - a Study with Pet." Proceedings of the Royal Society of London Series B-Biological Sciences **244**(1311): 241-246.
Gail, A. and R. A. Andersen (2006). "Neural dynamics in monkey parietal reach region reflect context-specific sensorimotor transformations." Journal of Neuroscience **26**(37): 9376-9384.
Galletti, C., D. F. Kutz, et al. (2003). "Role of the medial parieto-occipital cortex in the control of reaching and grasping movements." Experimental Brain Research **153**(2): 158-170.
Garavan, H., T. J. Ross, et al. (2003). "A midline dissociation between error-processing and response-conflict monitoring." Neuroimage **20**(2): 1132-1139.
Garavan, H., T. J. Ross, et al. (1999). "Right hemispheric dominance of inhibitory control: An event-related functional MRI study." Proceedings of the National Academy of Sciences of the United States of America **96**(14): 8301-8306.
Gauthier, L., F. Dehaut, et al. (1989). "The Bells test." International Journal of Clinical Neuropsychology **11**: 49-54.
Gehring, W. J. and D. E. Fencsik (2001). "Functions of the medial frontal cortex in the processing of conflict and errors." Journal of Neuroscience **21**(23): 9430-9437.
Ghosh, S. and R. Gattera (1995). "A comparison of the ipsilateral cortical projections to the dorsal and ventral subdivisions of the macaque premotor cortex." Somatosensory motor research **12**(3-4): 359-78.
Glimcher, P. W. (2003). "The neurobiology of visual-saccadic decision making." Annual Review of Neuroscience **26**(1): 133-179.
Glover, S., R. C. Miall, et al. (2005). "Parietal rTMS disrupts the initiation but not the execution of on-line adjustments to a perturbation of object size." Journal of Cognitive Neuroscience **17**(1): 124-136.

Goldberg, M. E., J. Bisley, et al. (2002). "The role of the lateral intraparietal area of the monkey in the generation of saccades and visuospatial attention." Annals of New York Academy of Science **956**: 205-215.
Goldberg, M. E., J. W. Bisley, et al. (2006). Saccades, salience and attention: the role of the lateral intraparietal area in visual behavior. Visual Perception, Pt 2: Fundamentals of Awareness: Multi-Sensory Integration and High-Order Perception. **155:** 157-175.
Goldenberg, G. (1999). "Matching and imitation of hand and finger postures in patients with damage in the left or right hemispheres." Neuropsychologia **37**(5): 559-66.
Gottlieb, J. (2001). "Parietal mechanisms of target representation." Current Opinion in Neurobiology **12**: 134-140.
Gottlieb, J. (2007). "From thought to action: The parietal cortex as a bridge between perception, action, and cognition." Neuron **53**(1): 9-16.
Gottlieb, J. P., M. Kusunoki, et al. (1998). "The representation of visual salience in monkey parietal cortex." Nature **391**: 481-484.
Gratton, G., M. G. H. Coles, et al. (1992). "Optimizing the use of information: strategic control of activation of responses." J. Exp. Psychol. **4**: 480-506.
Grefkes, C. and G. R. Fink (2005). "The functional organization of the intraparietal sulcus in humans and monkeys." Journal of Anatomy **207**(1): 3-17.
Hartje, W. and G. Ettlinger (1973). "Reaching in light and dark after unilateral posterior parietal ablations." Cortex **9**: 346-354.
Harvey, M. (2004). "Perceptual and premotor neglect: Is there an ideal task to categorise patients?" Cortex **40**: 323-328.
Harvey, M., T. Kramer-McCaffery, et al. (2002). "Categorisation of 'perceptual' and 'premotor' neglect patients across different tasks: is there strong evidence for a dichotomy?" Neuropsychologia **40**(8): 1387-1395.
Harvey, M., A. D. Milner, et al. (1994). "Spatial Bias in Visually-Guided Reaching and Bisection Following Right Cerebral Stroke." Cortex **30**(2): 343-350.
Harvey, M., A. D. Milner, et al. (1995). "An Investigation of Hemispatial Neglect Using the Landmark Task." Brain and Cognition **27**(1): 59-78.
Heide, W., M. Blankenburg, et al. (1995). "Cortical control of double-step saccades: Implications for spatial orientation." Ann Neurol **38**: 739-748.
Heilman, K. M. and T. V. D. Abell (1980). "Right hemisphere dominance for attention: The mechanism underlying hemispheric asymmetries of inattention (neglect)." Neurology **30**(3): 327-.
Heilman, K. M., D. Bowers, et al. (1985). "Directional hypokinesia: prolonged reaction times for leftward movements in patients with right hemisphere lesions and neglect." Neurology **35**: 855-859.
Heilman, K. M., E. Valenstein, et al. (1995). "Frontal lobe neglect in monkeys." Neurology **45**(6): 1205-10.
Heilman, K. M. and T. Vandenabell (1980). "Right-Hemisphere Dominance for Attention - Mechanism Underlying Hemispheric Asymmetries of Inattention (Neglect)." Neurology **30**(3): 327-330.
Hillis, A. E. (2006). "Neurobiology of Unilateral Spatial Neglect." Neuroscientist **12**(2): 153-163.
Hillis, A. E., M. Newhart, et al. (2005). "Anatomy of spatial attention: insights from perfusion imaging and hemispatial neglect in acute stroke." J Neurosci **25**(12): 3161-7.

Hodges, N. J., J. Lyons, et al. (1997). "Hand, space and attentional asymmetries in goal-directed manual aiming." Cortex **33**(2): 251-269.
Howes, D. and F. Boller (1975). "Simple reaction time: evidence for focal impairment from lesions of the right hemisphere." Brain **98**(2): 317-332.
Humphreys, G. (2001). "Objects, affordances...action! ." The Psychologist **14**(8): 408-412.
Humphreys, G. W. and M. Jane Riddoch (2001). "Detection by action: neuropsychological evidence for action-defined templates in search." Nat Neurosci **4**(1): 84-88.
Husain, M. and C. Kennard (1997). "Distractor-dependent frontal neglect." Neuropsychologia **35**(6): 829-41.
Husain, M., J. B. Mattingley, et al. (2000). "Distinguishing sensory and motor biases in parietal and frontal neglect." Brain **123**: 1643-59.
Husain, M. and P. Nachev (2007). "Space and the parietal cortex." Trends in Cognitive Sciences **11**: 30-36.
Husain, M. and C. Rorden (2003). "Non-spatially lateralized mechanisms in hemispatial neglect." Nat Rev Neurosci **4**(1): 26-36.
Jackson, S. R., R. Newport, et al. (2000). "Reaching movements may reveal the distorted topography of spatial representations after neglect." Neuropsychologia **38**(4): 500-507.
Jahanshahi, M., H. Jenkins, et al. (1995). "Self-Initiated Versus Externally Triggered Movements .1. an Investigation Using Measurement of Regional Cerebral Blood-Flow with Pet and Movement-Related Potentials in Normal and Parkinsons-Disease Subjects." Brain **118**: 913-933.
Karnath, H.-O. and M.-T. Perenin (2005). "Cortical Control of Visually Guided Reaching: Evidence from Patients with Optic Ataxia." Cereb. Cortex: bhi034.
Karnath, H. O., M. Fruhmann Berger, et al. (2004). "The anatomy of spatial neglect based on voxelwise statistical analysis: a study of 140 patients." Cereb Cortex **14**(10): 1164-72.
Karnath, H. O., M. Himmelbach, et al. (2002). "The subcortical anatomy of human spatial neglect: putamen, caudate nucleus and pulvinar." Brain **125**(Pt 2): 350-60.
Kawashima, R., K. Yamada, et al. (1993). "Regional cerebral blood flow changes of cortical motor areas and prefrontal areas in humans related to ipsilateral and contralateral hand movement." Brain Research **623**(1): 33-40.
Keller, P. E., E. Wascher, et al. (2006). "Differences between intention-based and stimulus-based actions." Journal of Psychophysiology **20**(1): 9-20.
Kerns, J. G., J. D. Cohen, et al. (2004). "Anterior Cingulate conflict monitoring and adjustments in control." Science **303**(5660): 1023-1026.
Khan, A. Z., L. Pisella, et al. (2005). "Optic ataxia errors depend on remapped, not viewed, target location." Nature Neuroscience **8**(4): 418-420.
Kiesel, A., A. Wagener, et al. (2006). "Unconscious manipulation of free choice in humans." Consciousness and Cognition **15**(2): 397-408.
Kimura, D. (1982). "Left-Hemisphere Control of Oral and Brachial Movements and Their Relation to Communication." Philosophical Transactions of the Royal Society of London Series B-Biological Sciences **298**(1089): 135-149.
Kimura, m. and Y. Archibald (1974). "Motor functions of the left hemisphere." Brain **97**: 337-350.

Klapp, S. T. and L. B. Hinkley (2002). "The negative compatibility effect: unconscious inhibition influences reaction time and response selection." Journal of Experimental Psychology: General **131**(2): 255-269.
Konishi, S., K. Nakajima, et al. (1999). "Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related functional MRI." Brain **122**: 981-991.
Ladavas, E., C. Umilta, et al. (1993). "The role of right side objects in left side neglect: A dissociation between perceptual and directional motor neglect." Neuropsychologia **31**(8): 761-773.
Lamotte, R. H. and C. Acuna (1978). "Defects in accuracy of reaching after removal of posterior parietal cortex in monkeys." Brain Res **139**: 309-326.
Laplane, D. and J. D. Degos (1983). "Motor Neglect." Journal of Neurology Neurosurgery and Psychiatry **46**(2): 152-158.
Lau, H., R. D. Rogers, et al. (2006). "Dissociating response selection and conflict in the medial frontal surface." Neuroimage **29**(2): 446-451.
Lau, H., R. D. Rogers, et al. (2004). "Willed action and attention to the selection of action." NeuroImage **21**: 1407-1415.
Lavie, N. and I. H. Robertson (2001). "The Role of Perceptual Load in Neglect: Rejection of Ipsilesional Distractors is Facilitated with Higher Central Load." Journal of Cognitive Neuroscience **13**(7): 867-876.
Liston, C., S. Matalon, et al. (2006). "Anterior cingulate and posterior parietal cortices are sensitive to dissociable forms of conflict in a task-switching paradigm." Neuron **50**(4): 643-653.
Lleras, A. and J. T. Enns (2004). "Negative Compatibility or object updating? A cautionary tale of mask-dependent priming." Journal of Experimental Psychology: general **133**(4): 475-493.
Lupianez, J., C. Decaix, et al. (2004). "Independent effects of endogenous and exogenous spatial cueing: inhibition of return at endogenously attended target locations." Exp Brain Res **159**: 447-457.
MacDonald, A. W., J. D. Cohen, et al. (2000). "Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control." Science **288**(5472): 1835-1838.
Machado, L., N. Wyatt, et al. (2007). "Action planning in the presence of distracting stimuli: an investigation into the time course of distractor effects." J Exp Psychol Hum Percept Perform **33**(5): 1045-1061.
Malhotra, P., R. Greenwood, et al. (2004). "The diagnosis of spatial neglect in acute stroke." Journal of Neurology, Neurosurgery, and Psychiatry **75**: 521.
Malhotra, P., S. Mannan, et al. (2004). "Impaired spatial working memory: One component of the visual neglect syndrome?" Cortex **40**: 667-676.
Malhotra, P., A. Parton, et al. (2003). "A spatial memory deficit exacerbates visual neglect following stroke." Journal of Neurology, Neurosurgery, and Psychiatry **74**: 403.
Mannan, S., D. Mort, et al. (2005). "Revisiting previously searched locations in visual neglect: Role of right parietal and frontal lesions in misjudging old locations as new." Journal of Cognitive Neuroscience **17**: 340-354.
Marotta, J. J., T. J. McKeeff, et al. (2003). "Hemispatial neglect: its effects on visual perception and visually guided grasping." Neuropsychologia **41**(9): 1262-1271.
Marteniuk, R., C. Mackenzie, et al. (1987). "Constraints on human arm movements trajectories." Canadian Journal of Psychology-Revue Canadienne De Psychologie **41**(3): 365-78.

Mattingley, J. B., J. L. Bradshaw, et al. (1992). "Impairments of movement initiation and execution in unilateral neglect. Directional hypokinesia and bradykinesia." Brain **115 (Pt 6)**: 1849-74.
Mattingley, J. B., L. A. Corben, et al. (1998). "The effects of competition and motor reprogramming on visuomotor selection in unilateral neglect." Exp Brain Res **120**(2): 243-56.
Mattingley, J. B. and J. Driver (1997). "Distinguishing sensory and motor deficits after parietal damage: an evaluation of response selection biases in unilateral neglect." Thier P, Karnath H, editors. Parietal contributions to orientaion in 3D space. Heidelberg Springer.: 309-338.
Mattingley, J. B., M. Husain, et al. (1998). "Motor role of human inferior parietal lobe revealed in unilateral neglect patients." Nature **392**(6672): 179-82.
Mattingley, J. B., J. G. Phillips, et al. (1994). "Impairments of movement execution in unilateral neglect: a kinematic analysis of directional bradykinesia." Neuropsychologia **32**(9): 1111-34.
Mattler, U. (2006). "Distance and ratio effects in the flanker task are due to different mechanisms." Q J Exp Psychol A **59**(10): 1745-1763.
Mayr, U. U., E. E. Awh, et al. (2003). "Conflict adaptation effects in the absence of executive control." Nature Neuroscience **6**(5): 450-2.
McIntosh, R. D., K. I. McClements, et al. (2004). "Avoidance of obstacles in the absence of visual awareness." Proceedings of the Royal Society of London Series B-Biological Sciences **271**(1534): 15-20.
Mead, L. A., A. R. Mayer, et al. (2002). "Neural basis of the Stroop interference task: Response competition or selective attention?" Journal of the International Neuropsychological Society **8**(6): 735-742.
Medendorp, W. P., H. C. Goltz, et al. (2003). "Gaze-centered updating of visual space in human parietal cortex." Journal of Neuroscience **23**(15): 6209-6214.
Medendorp, W. P., M. A. Smith, et al. (2002). "Rotational remapping in human spatial memory during eye and head motion." Journal of Neuroscience **22**(1): art. no.-RC196.
Merriam, E. P., C. R. Genovese, et al. (2003). "Spatial updating in human parietal cortex." Neuron **39**(2): 361-373.
Mesulam, M. (1985). "Patterns in behavioural neuroanatomy:association areas, the limbic system and hemispheric specialization." F.A. Davis Co, Principles of behavioural neurology, Philadelphia **1-70**.
Mesulam, M. M. (1981). "A cortical network for directed attention and unilateral neglect." Ann Neurol **10**(4): 309-25.
Mesulam, M. M. (1999). "Spatial attention and neglect: parietal, frontal and cingulate contributions to the mental representation and attentional targeting of salient extrapersonal events." Philos Trans R Soc Lond B Biol Sci **354**(1387): 1325-46.
Milea, D., E. Lobel, et al. (2007). "Prefrontal cortex is involved in internal decision of forthcoming saccades." Neuroreport **18**(12): 1221-1224.
Milham, M. P., M. T. Banich, et al. (2003). "Practice-related effects demonstrate complementary roles of anterior cingulate and prefrontal cortices in attentional control." Neuroimage **18**(2): 483-493.
Miller, E. K. and J. D. Cohen (2001). "An integrative theory of prefrontal cortex function." Annual Review of Neuroscience **24**: 167-202.
Milner, A. D. and M. A. Goodale (1995). The Visual Brain in Action. Oxford, Oxford University Press.

Milner, A. D., M. Harvey, et al. (1993). "Line Bisection Errors in Visual Neglect - Misguided Action or Size Distortion." Neuropsychologia **31**(1): 39-49.
Mort, D. J., P. Malhotra, et al. (2003). "The anatomy of visual neglect." Brain **126**(Pt 9): 1986-97.
Mueller, V. A., M. Brass, et al. (2007). "The role of the preSMA and the rostral cingulate zone in internally selected actions." NeuroImage **38**: 1354-1361.
Nachev, P., G. Rees, et al. (2005). "Volition and conflict in human medial frontal cortex." Current Biology **15**(2): 122-128.
Nachev, P., H. Wydell, et al. (2007). "The role of the pre-supplementary motor area in the control of action." Neuroimage **36**: T155-T163.
Nakano, K., Y. Hasegawa, et al. (1993). "Cortical connections of the motor thalamic nuclei in the Japanese monkey, Macaca fuscata." Stereotactic and functional neurosurgery **60**(60): 42-61.
Nico, D. (1996). "Detecting directional hypokinesia: The epidiascope technique." Neuropsychologia **34**(5): 471-474.
Niemeier, M. and H. O. Karnath (2000). "Exploratory saccades show no direction-specific deficit in neglect." Neurology **54**(2): 515-8.
Norman, D. and T. Shallice (1986). "Attention to action: Willed and automatic control of behavior." Consciousness and self-regulation: Advances in research and theory **4**(Davidson, R., Schwartz, G., and Shapiro, D., (eds). Plenum, New York, NY): 1-18.
Ogawa, K. and T. Inui (2007). "Lateralization of the Posterior Parietal Cortex for Internal Monitoring of Self- versus Externally Generated Movements." J. Cogn. Neurosci. **19**(11): 1827-1835.
Parris, B. A., N. J. Thai, et al. (2007). "The Role of the Lateral Prefrontal Cortex and Anterior Cingulate in Stimulus-Response Association Reversals." Journal of Cognitive Neuroscience **19**(1): 13-24.
Passingham, R. E. (1993). "The frontal lobes and voluntary action." Oxford University Press, Oxford.
Paus, T. (2001). "Primate anterior cingulate cortex: where motor control, drive and cognition interface." Nature Reviews Neuroscience **2**: 417-424.
Picard, N. and P. L. Strick (2001). "Imaging the premotor areas." Curr Opin Neurobiol **11**(6): 663-72.
Pisella, L., H. Grea, et al. (2000). "An 'automatic pilot' for the hand in human posterior parietal cortex: toward reinterpreting optic ataxia." Nat Neurosci **3**(7): 729-36.
Platt, M. L. and P. W. Glimcher (1999). "Neural correlates of decision variables in parietal cortex." Nature **400**(6741): 233-238.
Playford, E. D., I. H. Jenkins, et al. (1992). "Impaired Mesial Frontal and Putamen Activation in Parkinsons-Disease - a Positron Emission Tomography Study." Annals of Neurology **32**(2): 151-161.
Posner, M. I. and G. J. DiGirolamo (1998). "Executive attention: conflict, target detection, and cognitive control In: R. Parasuraman, Editors, The Attentive Brain." MIT Press **Cambridge, MA**: 401-423.
Posner, M. I., R. Rafal, et al. (1985). "Inhibition of return: neural basis and function." Cogn Neuropsychol **2**(211-228).
Posner, M. I., J. A. Walker, et al. (1984). "Effects of parietal injury on covert orienting of attention." Journal of Neuroscience **4**: 1863-1874.
Pouget, A. and J. Driver (2000). "Relating unilateral neglect to the neural coding of space." Curr Opin Neurobiol **10**(2): 242-9.

Pritchard, C. L., A. D. Milner, et al. (1997). "Visuospatial neglect: Veridical coding of size for grasping but not for perception." Neurocase **3**(6): 437-443.
Procyk, E. and P. S. Goldman-Rakic (2006). "Modulation of dorsolateral prefrontal delay activity during self-organized behavior." Journal of Neuroscience **26**(44): 11313-11323.
Pujol, J., P. Vendrell, et al. (2001). "The effect of medial frontal and posterior parietal demyelinating lesions on stroop interference." Neuroimage **13**(1): 68-75.
Punt, T. D. and M. J. Riddoch (2006). "Motor neglect: Implications for movement and rehabilitation following stroke." Disability and Rehabilitation **28**(13-14): 857-864.
Punt, T. D., M. J. Riddoch, et al. (2005). "Bimanual coordination and perceptual grouping in a patient with motor neglect." Cognitive Neuropsychology **22**(7): 795-815.
Punt, T. D., M. J. Riddoch, et al. (2005). "Don't think twice, it's all right--contralesional dependency for bimanual prehension movements." Neuropsychologia **43**(11): 1547-1558.
Ridderinkhof, K. R., M. Ullsperger, et al. (2004). "The role of the medial frontal cortex in cognitive control." Science **306**(5695): 443-7.
Ridderinkhof, K. R., W. P. M. van den Wildenberg, et al. (2004). "Neurocognitive mechanisms of cognitive control: The role of prefrontal cortex in action selection, response inhibition, performance monitoring, and reward-based learning." Brain and Cognition **56**(2): 129-140.
Rizzolatti, G. and G. Luppino (2001). "The cortical motor system." Neuron **31**(6): 889-901.
Ro, T., Y. E. Cohen, et al. (1998). "Response channel activation and the temporoparietal junction." Brain and cognition **37**: 461-476.
Robertson, I. H., T. Manly, et al. (1997). "Auditory sustained attention is a marker of unilateral spatial neglect." Neuropsychologia **35**(12): 1527-32.
Robertson, I. H., D. Nico, et al. (1995). "The intention to act improves unilateral left neglect: Two demonstrations." Neuroreport **7**(1): 246-248.
Robertson, L. C. (2003). "Space, Objects, Minds and Brains." New York: Psychology Press: Essays in Cognitive Science.
Rorden, C., L. Bonilha, et al. (2007). "Rank-order versus mean based statistics for neuroimaging." NeuroImage **35**(4): 1531-1537.
Rorden, C., M. Fruhmann Berger, et al. (2006). "Disturbed line bisection is associated with posterior brain lesions." Brain Research **1080**(1): 17-25.
Rorden, C., H.-O. Karnath, et al. (2007). "Improving Lesion-Symptom Mapping." J. Cogn. Neurosci. **19**(7): 1081-1088.
Rorie, A. E. and W. T. Newsome (2005). "A general mechanism for decision-making in the human brain?" Trends in Cognitive Sciences **9**(2): 41-43.
Rozzi, S., R. Calzavara, et al. (2006). "Cortical connections of the inferior parietal cortical convexity of the macaque monkey." Cereb Cortex **16**: 1389-1417.
Rueckart, L. and J. Grafman (1996). "Sustained attention deficits in patients with right frontal lesions." Neuropsychologia **34**: 953-963.
Rushworth, M. F., M. E. Walton, et al. (2004). "Action sets and decisions in the medial frontal cortex." Trends Cogn Sci **8**(9): 410-417.
Rushworth, M. F. S., A. Ellison, et al. (2001). "Complementary localization and lateralization of orienting and motor attention." Nat Neurosci **4**(6): 656-661.

Rushworth, M. F. S., K. A. Hadland, et al. (2003). "The effect of cingulate cortex lesions on task switching and working memory." Journal of Cognitive Neuroscience **15**(3): 338-353.
Rushworth, M. F. S., H. Johansen-Berg, et al. (2003). "The left parietal and premotor cortices: motor attention and selection." Neuroimage **20**: S89-S100.
Rushworth, M. F. S., M. Krams, et al. (2001). "The attentional role of the left parietal cortex: The distinct lateralization and localization of motor attention in the human brain." Journal of Cognitive Neuroscience **13**(5): 698-710.
Rushworth, M. F. S., M. E. Walton, et al. (2004). "Action sets and decisions in the medial frontal cortex." Trends in Cognitive Sciences **8**(9): 410-417.
Sakai, K., J. B. Rowe, et al. (2002). "Active maintenance in prefrontal area 46 creates distractor-resistant memory." Nat Neurosci **5**(5): 479-84.
Sapir, A., J. B. Kaplan, et al. (2007). "Anatomical correlates of directional hypokinesia in patients with hemispatial neglect." Journal of Neuroscience **27**(15): 4045-4051.
Scerif, G., M. S. Worden, et al. (2006). "Context modulates early stimulus processing when resolving stimulus-response conflict." Journal of Cognitive Neuroscience **18**(5): 781-792.
Scherberger, H. and R. A. Andersen (2007). "Target selection signals for arm reaching in the posterior parietal cortex." Journal of Neuroscience **27**(8): 2001-2012.
Schlaghecken, F. and M. Eimer (1997). "The influence of subliminally presented primes on response preparation." Sprache & Kognition **16**(3-4): 166-175.
Schlaghecken, F. and M. Eimer (2004). "Masked prime stimuli can bias "free" choices between response alternatives." Psychonomic Bulletin & Review **11**(3): 463-468.
Schlaghecken, F. and E. A. Maylor (2005). "Motor control in old age: evidence of impaired low-level inhibition." Journal of Gerontology: Psychological Sciences **60B**(3): 158-161.
Schmahmann, J. D., D. N. Pandya, et al. (2007). "Association fibre pathways of the brain: parallel observations from diffusion spectrum imaging and autoradiography." Brain **130**(3): 630-653.
Seiss, E. and P. Praamstra (2004). "The basal ganglia and inhibitory mechanisms in response selection: evidence from subliminal priming of motor responses in Parkinson's disease." Brain **127**: 330-339.
Seiss, E. and P. Praamstra (2006). "Time-course of masked response priming and inhibition in Parkinson's disease." Neuropsychologia **44**: 869-875.
Serrien, D. J., R. B. Ivry, et al. (2006). "Dynamics of hemispheric specialization and integration in the context of motor control." Nat Rev Neurosci **7**(2): 160-166.
Sheskin, J. (2007). "Handbook of parametric and nonparametric statistical procedures." Chapman and Hall/CRC **4 Ed.**
Siekierka-Kleiser, E. M., R. Kleiser, et al. (2006). "Quantitative Assessment of Recovery from Motor Hemineglect in Acute Stroke Patients." Cerebrovascular diseases **21**: 307-314.
Smith, P. L. and R. Ratcliff (2004). "Psychology and neurobiology of simple decisions." Trends in Neurosciences **27**(3): 161-168.
Snodgrass, J. G. and J. Corwin (1988). "Pragmatics of measuring recognition memory: applications to dementia and amnesia." J Exp Psychol Gen **117**(1): 34-50.

Snow, J. C. and J. B. Mattingley (2006). "Goal-driven selective attention in patients with right hemisphere lesions: how intact is the ipsilesional field?" Brain **129**(1): 168-181.
Snyder, L. H., A. P. Batista, et al. (1997). "Coding of intention in the posterior parietal cortex." Nature **386**(6621): 167-70.
Stein, J. (1978). "Effects of parietal lobe cooling on manipulative behaviour in the conscious monkey." In Active Touch. The mechanisms of recognition of objects by manipulation: a multidisciplinary approach. ed. gordon, G. Oxford: Pergamon Press: 79-90.
Stein, J. F. and M. Glickstein (1992). "Role of the Cerebellum in Visual Guidance of Movement." Physiological Reviews **72**(4): 967-1017.
Stoet, G. and L. H. Snyder (2004). "Single neurons in posterior parietal cortex of monkeys encode cognitive set." Neuron **42**: 1003-1012.
Stoet, G. and L. H. Snyder (2007). "Correlates of stimulus-response congruence in the posterior parietal cortex." J Cogn Neurosci **19**(2): 194-203.
Stone, S. P., P. W. Halligan, et al. (1993). "The incidence of neglect phenomena and related disorders in patients with an acute right or left hemisphere stroke." Age Ageing **22**(1): 46-52.
Stone, S. P., B. Wilson, et al. (1991). "The assessment of visuo-spatial neglect after acute stroke." J Neurol Neurosurg Psychiatry **54**(4): 345-50.
Stuss, D. T., S. M. Bisschop, et al. (2001). "Stroop performance in focal lesion patients: dissociation of processes and frontal lobe lesion location." Neuropsychologia **39**: 771-786.
Sugrue, L. P., G. S. Corrado, et al. (2004). "Matching behavior and the representation of value in the parietal cortex." Science **304**(5678): 1782-1787.
Sugrue, L. P., G. S. Corrado, et al. (2005). "Choosing the greater of two goods: Neural currencies for valuation and decision making." Nature Reviews Neuroscience **6**(5): 363-375.
Sumner, P. (2007). "Negative and positive masking-priming - implications for motor inhibition." Advances in Cognitive Psychology **3**: 317-326.
Sumner, P. (2008). "Mask-induced priming and the negative compatibility effect." Experimental Psychology **55**: 133-41.
Sumner, P. and M. Husain (2007). "At the edge of consciousness: automatic motor activation and voluntary control." Neuroscientist **In press**.
Sumner, P., P. Nachev, et al. (2007). "Human Medial Frontal Cortex Mediates Unconscious Inhibition of Voluntary Action." Neuron **54**(5): 697-711.
Sumner, P., P.-C. Tsai, et al. (2006). "Attentional modulation of sensorimotor processes in the absence of perceptual awareness." Proceedings of the National Academy of Sciences **103**(27): 10520-10525.
Swainson, R., R. Cunnington, et al. (2003). "Cognitive control mechanisms revealed by ERP and fMRI: Evidence from repeated task-switching." Journal of Cognitive Neuroscience **15**(6): 785-799.
Swick, D. and J. Jovanovic (2002). "Anterior cingulate cortex and the Stroop task: neuropsychological evidence for topographic specificity." Neuropsychologia **40**(8): 1240-1253.
Swick, D. and U. Turken (2002). "Dissociation between conflict detection and error monitoring in the human anterior cingulate cortex." Proceedings of the National Academy of Sciences of the United States of America **99**(25): 16354-16359.

Tegner, R. and M. Levander (1991). "Through a looking glass. A new technique to demonstrate directional hypokinesia in unilateral neglect." Brain **114**: 1943-1951.
Toga, A. W. and P. M. Thompson (2003). "Mapping brain asymmetry." Nat Rev Neurosci **4**(1): 37-48.
Triggs, W. J., M. Gold, et al. (1994). "Motor neglect associated with a discrete parietal lesion." Neurology **44**(6): 1164-.
Tunik, E., S. H. Frey, et al. (2005). "Virtual lesions of the anterior intraparietal area disrupt goal-dependent on-line adjustments of grasp." Nature Neuroscience **8**(4): 505-511.
Turken, A. U. and D. Swick (1999). "Response selection in the human anterior cingulate cortex." Nature Neuroscience **2**: 920-924.
Ullsperger, M., L. M. Bylsma, et al. (2005). "The conflict adaptation effect: It's not just priming." Cognitive Affective & Behavioral Neuroscience **5**(4): 467-472.
Ullsperger, M. and D. Y. von Cramon (2001). "Subprocesses of performance monitoring: A dissociation of error processing and response competition revealed by event-related fMRI and ERPs." Neuroimage **14**(6): 1387-1401.
Ullsperger, M. and D. Y. von Cramon (2004). "Neuroimaging of performance monitoring: error detection and beyond." Cortex **40**(4-5): 593-604.
Ullsperger, M., D. Y. von Cramon, et al. (2002). "Interactions of focal cortical lesions with error processing: evidence from event-related brain potentials." Neuropsychology **16**(4): 548-61.
Ullsperger, M. and D. Yves von Cramon (2006). "The role of intact frontostriatal circuits in error processing." Journal of Cognitive Neuroscience **18**: 651-664.
Valenstein, E. and K. M. Heilman (1981). "Unilateral hypokinesia and motor extinction." Neurology **31**(4): 445-.
Vallar, G. and D. Perani (1986). "The anatomy of unilateral neglect after right-hemisphere stroke lesions. A clinical/CT-scan correlation study in man." Neuropsychologia **24**(5): 609-22.
van Veen, V. and C. S. Carter (2002). "The timing of action-monitoring processes in the anterior cingulate cortex." Journal of Cognitive Neuroscience **14**(4): 593-602.
van Veen, V. and C. S. Carter (2005). "Separating semantic conflict and response conflict in the Stroop task: A functional MRI study." Neuroimage **27**(3): 497-504.
van Veen, V., J. D. Cohen, et al. (2001). "Anterior cingulate cortex, conflict monitoring, and levels of processing." Neuroimage **14**(6): 1302-1308.
van Veen, V., C. B. Holroyd, et al. (2004). "Errors without conflict: Implications for performance monitoring theories of anterior cingulate cortex." Brain and Cognition **56**(2): 267-276.
Vilkki, J. (1984). "Visual hemi-inattention after ventrolateral thalamotomy." Neuropsychologia **22**(4): 399-408.
von Giesen, H.-J., G. Schlaug, et al. (1994). "Cerebral network underlying unilateral motor neglect: evidence from positron emission tomography." Journal of the Neurological Sciences **125**(1): 29-38.
Walker, R., S. K. Mannan, et al. (2000). "The oculomotor distractor effect in normal and hemianopic vision." Proc R Soc Lond B Biol Sci **267**(1442): 431.
Wardak, C., E. Olivier, et al. (2004). "A deficit in covert attention after parietal cortex inactivation in the monkey." Neuron **42**(3): 501-8.

Wascher, E., M. Reinhard, et al. (1999). "Spatial S-R compatibility with centrally presented stimuli: An event-related asymmetry study on dimensional overlap." Journal of Cognitive Neuroscience **11**(2): 214-229.
Waszak, F., E. Wascher, et al. (2005). "Intention-based and stimulus-based mechanisms in action selection." Experimental Brain Research **162**(3): 346-356.
Wilson, B., J. Cockburn, et al. (1987). Behavioural inattention test. Bury St. Edmunds, Thames Valley.
Wolf, S. L., C. J. Winstein, et al. (2006). "Effect of Constraint-Induced Movement Therapy on Upper Extremity Function 3 to 9 Months After Stroke: The EXCITE Randomized Clinical Trial." JAMA **296**(17): 2095-2104.
Wolpert, D. M. (1997). "Computational approaches to motor control." Trends in Cognitive Sciences **1**(6): 209-216.
Wolpert, D. M. and Z. Ghahramani (2000). "Computational principles of movement neuroscience."
Wolpert, D. M., S. J. Goodbody, et al. (1998). "Maintaining internal representations: the role of the human superior parietal lobe." Nat Neurosci **1**(6): 529-33.
Yang, T. and M. N. Shadlen (2007). "Probabilistic reasoning by neurons." Nature **447**(7148): 1075-1080.

Appendix 1 Movement execution deficits in neglect

While many studies have shown that movement execution is not normal in patients with neglect, the nature of the abnormality has been controversial. Directional slowing of movement execution similar to that found in movement initiation has been investigated by several groups. Heilman et al. found that once initiated, left neglect patients were slower than normal controls or subjects with left hemisphere damage to execute the movement (Heilman, Bowers et al. 1985), but the impairment in movement execution was not directional and was evident on both sides of space. However, some subsequent studies have reported directional deficits in movement execution (Mattingley, Bradshaw et al. 1992; Behrmann and Meegan 1998). For example, the sequential pressing task used by Mattingley and colleagues revealed that neglect patients with frontal or subcortical involvement were slower to execute leftward movements than rightward ones – a deficit the authors termed 'directional bradykinesia' to contrast it to the initiation deficit implied by 'directional hypokinesia' (Mattingley, Bradshaw et al. 1992).

In the paradigm used to dissociate reach direction from target location (Mattingley, Husain et al. 1998; Husain, Mattingley et al. 2000), the parietal neglect patients showed a generalised non-directional slowing in movement similar to that reported by Heilman and colleagues whose patients all had some parietal involvement. In contrast, right frontal patients with neglect were found to have slow reaches to left targets regardless of whether the reach was leftward or rightward. So, like the deficit in movement initiation, this impairment in right frontal neglect patients does not appear to be a

directional motoric one, although it may still be due to a spatial deficit in visuomotor control.

Further investigation into movement execution in neglect has examined specific effects on the kinematic properties of reaching in these patients. The findings have been highly variable with most studies suggesting no directional impairment (Fisk and Goodale 1988; Mattingley, Phillips et al. 1994; Konczak and Kamath 1998), but perhaps some generalised slowing particularly towards the end of the movement, implying an abnormal reliance on terminal visual guidance (rather than feed-forward control). Farné and co-workers did report possible lateralised deficits in on-line control of movement (Farne, Roy et al. 2003). They observed that patients with right brain damage had prolonged movement execution times when an on-line change of plan was required to move to a left target but, importantly, this effect was not specific to patients with neglect (Farne, Roy et al. 2003).

Reach trajectory in neglect has also been a controversial topic (Harvey, Jackson et al. 2001; Himmelbach and Karnath 2003). Early studies suggested that right-hemisphere patients (without evidence of neglect on clinical tests at the time of testing) showed some deviation of reach trajectory to the right (Goodale, Milner et al. 1990; Harvey, Milner et al. 1994). When patients were required to bisect a line or reach towards a target with or without visual feedback (Harvey, Milner et al. 1994), right-hemisphere stroke patients deviated to the right in the initial stages of reach and then corrected in the later stages so they had preserved endpoint accuracy. The rightward

deviation in reach trajectory was present only when visual feedback was absent suggesting either a motoric deficit (in planning or forward control of the motor command) or impairment of proprioceptive feedback mechanisms. Both of these could in theory be compensated for to some extent by visual input.

Subsequent studies have reported no clear abnormality of reach trajectory in neglect, with or without vision (Karnath, Dick et al. 1997; Harvey, Jackson et al. 2001; McIntosh, Pritchard et al. 2001). However, inspection of Karnath and his colleagues' reach data suggests that some right-hemisphere neglect patients can show substantial curvature (see, for example, their Fig. 1), raising the possibility that the analytical methods used to compute trajectory deviation may be critical in determining whether a positive effect is found.

While the heterogeneity between studies could depend upon technical differences, it is also important to remember that one would expect patients with neglect caused by lesions in different brain areas to behave differently from one another. Jackson and colleagues reported just such variability between patients (Jackson, Newport et al. 2000). They studied reaching trajectories in three right-hemisphere stroke patients (two neglect and one recovered neglect) to right and left-sided targets under three conditions. In the first condition the subject could see both the target and his arm; in the second, the target was hidden from view and was defined proprioceptively by placing the left index finger at the position of the target, but out of sight; the

third condition was similar to the second, except that the subject was blind-folded, so he had no visual feedback about the path of the arm.

The patient with neglect following a temporo-parietal lesion had a rightward deviation of reach trajectory, whereas, the patient with neglect and an occipito-temporal infarct displayed a tendency to increased rightward or leftward trajectory curvature depending on the side of the lesion. Unlike normal controls who had similar hand path trajectories under all three conditions, the patients showed increased hand path curvature (deviation from centre to the right or the left) in the full vision condition, intermediate hand path curvature in the second condition where the reaching arm could be seen (but the target was defined proprioceptively) and least curvature in the third condition where there was no visual feedback. Endpoint accuracy was relatively preserved in all of these patients. These results suggest that impaired visual feedback during reach execution might be an important factor in determining the degree of curvature during the reach in these patients, but is sufficient to allow relatively good accuracy in finally getting the hand on to target (Jackson, Newport et al. 2000). In addition, although the direction of trajectory deviation appeared to vary according to lesion location, the degree of deviation under different conditions was abnormal but consistent across patients with neglect.

One study investigated reaching in both arms of a patient with left *motor neglect* (Punt, Riddoch et al. 2005). This patient had no evidence of visual neglect, but did display symptoms of motor extinction such that left arm use

dramatically reduced when during bimanual compared with unimanual activity. Kinematic and trajectory analysis of movement with each hand separately and then both hands together either to one or two targets was performed. The leftward slowing was generally much worse when bimanual reaches to two rather than single targets were required even when the spatial location of the target reach was controlled for. The kinematic study suggested that the hands performed similarly until the final stages of reach when the left hand began to slow far more than the right thus uncoupling their activity. The authors suggest that this patient resolved competition in favour of action plans for the right hand that in turn fed forward to bias perceptual processing towards the right hand thus slowing the left.

Note that no motor initiation slowing was found in this motor neglect patient unlike the patient described in section **1.21** (Valenstein and Heilman 1981). This difference could perhaps be explained by the fact that the patient described earlier with a motor initiation deficit had a lesion in the head of the right caudate nucleus, whereas, the patient described here with end-stage slowing had a more cortical lesion involving inferior frontal, middle frontal superior temporal gyri. It is possible that the clinical syndrome of motor neglect can result from several component deficits in a similar way to the syndrome of spatial neglect.

To summarise these disparate results, movement execution appears to be abnormal in patients with neglect. In particular, abnormal temporal dynamics (movement execution time) of reach execution appear to occur at the end–

stages of reach and may be associated with presence of neglect (Mattingley, Bradshaw et al. 1992). There is a suggestion that reach trajectory abnormalities relate to lesion location (for example Jackson et al (2000)). This may explain why group studies that have divided patients according to the presence or absence of neglect rather than the location of lesions may not have found consistent spatial reaching abnormalities.

References

Behrmann, M. and D. V. Meegan (1998). "Visuomotor processing in unilateral neglect." Conscious Cogn **7**(3): 381-409.

Farne, A., A. C. Roy, et al. (2003). "Visuo-motor control of the ipsilateral hand: evidence from right brain-damaged patients." Neuropsychologia **41**(6): 739-757.

Fisk, J. D. and M. A. Goodale (1988). "The Effects of Unilateral Brain-Damage on Visually Guided Reaching - Hemispheric-Differences in the Nature of the Deficit." Experimental Brain Research **72**(2): 425-435.

Goodale, M. A., A. D. Milner, et al. (1990). "Kinematic Analysis of Limb Movements in Neuropsychological Research - Subtle Deficits and Recovery of Function." Canadian Journal of Psychology-Revue Canadienne De Psychologie **44**(2): 180-195.

Harvey, M., S. R. Jackson, et al. (2001). "Is grasping impaired in hemispatial neglect?" Behavioural Neurology **13**(1-2): 17-28.

Harvey, M., A. D. Milner, et al. (1994). "Spatial Bias in Visually-Guided Reaching and Bisection Following Right Cerebral Stroke." Cortex **30**(2): 343-350.

Heilman, K. M., D. Bowers, et al. (1985). "Directional hypokinesia: prolonged reaction times for leftward movements in patients with right hemisphere lesions and neglect." Neurology **35**: 855-859.

Himmelbach, M. and H. O. Karnath (2003). "Goal-directed hand movements are not affected by the biased space representation in spatial neglect." Journal of Cognitive Neuroscience **15**(7): 972-980.

Husain, M., J. B. Mattingley, et al. (2000). "Distinguishing sensory and motor biases in parietal and frontal neglect." Brain **123**: 1643-59.

Jackson, S. R., R. Newport, et al. (2000). "Reaching movements may reveal the distorted topography of spatial representations after neglect." Neuropsychologia **38**(4): 500-507.

Karnath, H. O., H. Dick, et al. (1997). "Kinematics of goal-directed arm movements in neglect: control of hand in space." Neuropsychologia **35**(4): 435-44.

Konczak, J. and H. O. Kamath (1998). "Kinematics of goal-directed arm movements in neglect: Control of hand velocity." Brain and Cognition **37**(3): 387-403.

Mattingley, J. B., J. L. Bradshaw, et al. (1992). "Impairments of movement initiation and execution in unilateral neglect. Directional hypokinesia and bradykinesia." Brain **115 (Pt 6)**: 1849-74.

Mattingley, J. B., M. Husain, et al. (1998). "Motor role of human inferior parietal lobe revealed in unilateral neglect patients." Nature **392**(6672): 179-82.

Mattingley, J. B., J. G. Phillips, et al. (1994). "Impairments of movement execution in unilateral neglect: a kinematic analysis of directional bradykinesia." Neuropsychologia **32**(9): 1111-34.

McIntosh, R. D., C. L. Pritchard, et al. (2001). "Prehension and perception of size in left visual neglect." Behavioural Neurology **13**(1-2): 3-15.

Punt, T. D., M. J. Riddoch, et al. (2005). "Bimanual coordination and perceptual grouping in a patient with motor neglect." Cognitive Neuropsychology **22**(7): 795-815.

Valenstein, E. and K. M. Heilman (1981). "Unilateral hypokinesia and motor extinction." Neurology **31**(4): 445-.

Appendix 2

A2.1 Lesions for chapter 3

A2.1.1 PPC neglect patients

A2.1.2 Non-PPC neglect patients

A2.1.3 Left hemisphere patients

A2.1.4 Non-neglect patients

A2.2 Chapter 4 all patients

A2.3 Chapter 5

A2.3.1 Neglect patients

A2.3.2 Non-neglect patients

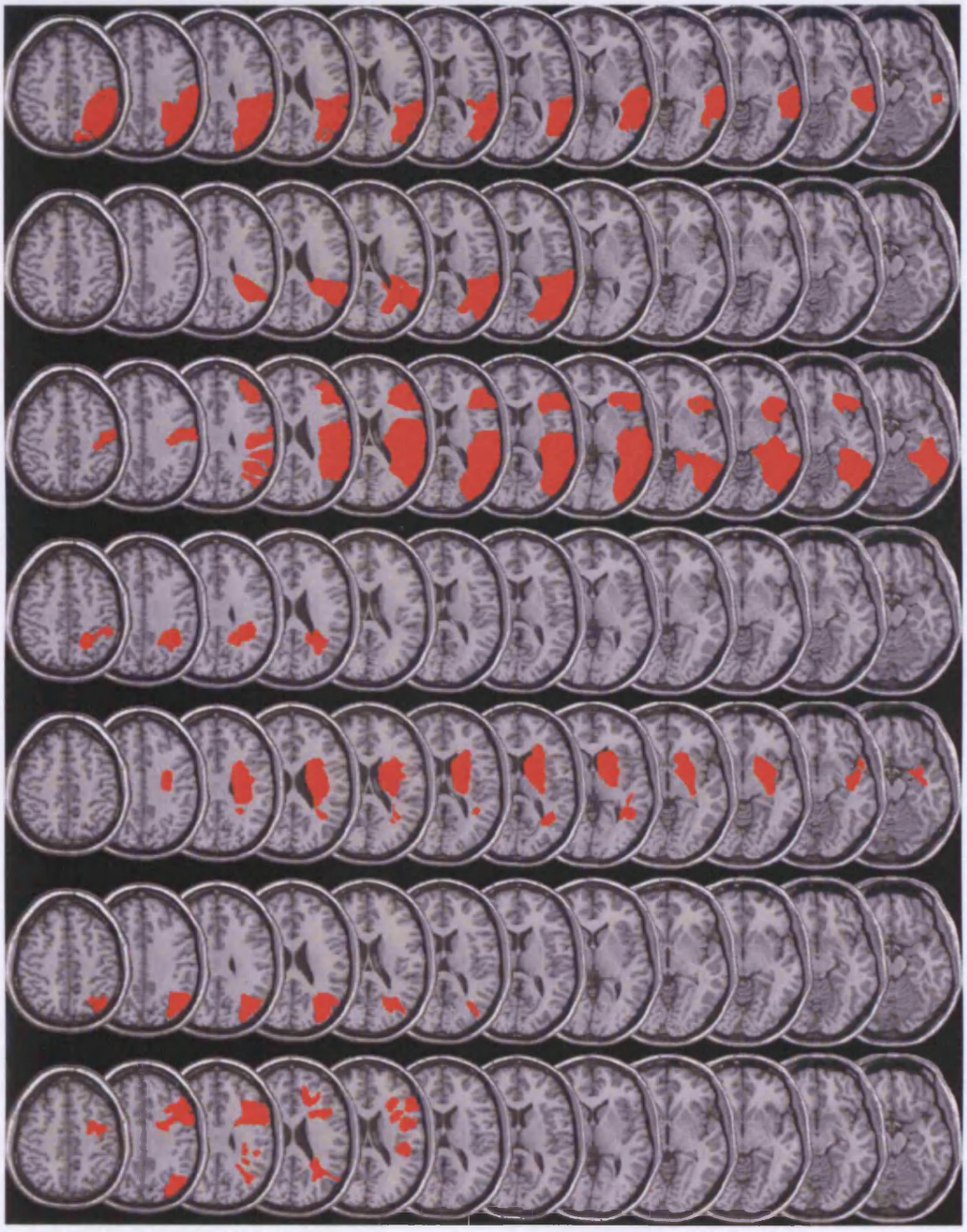
A2.4 Chapter 7

A2.4.1 Motor neglect patients

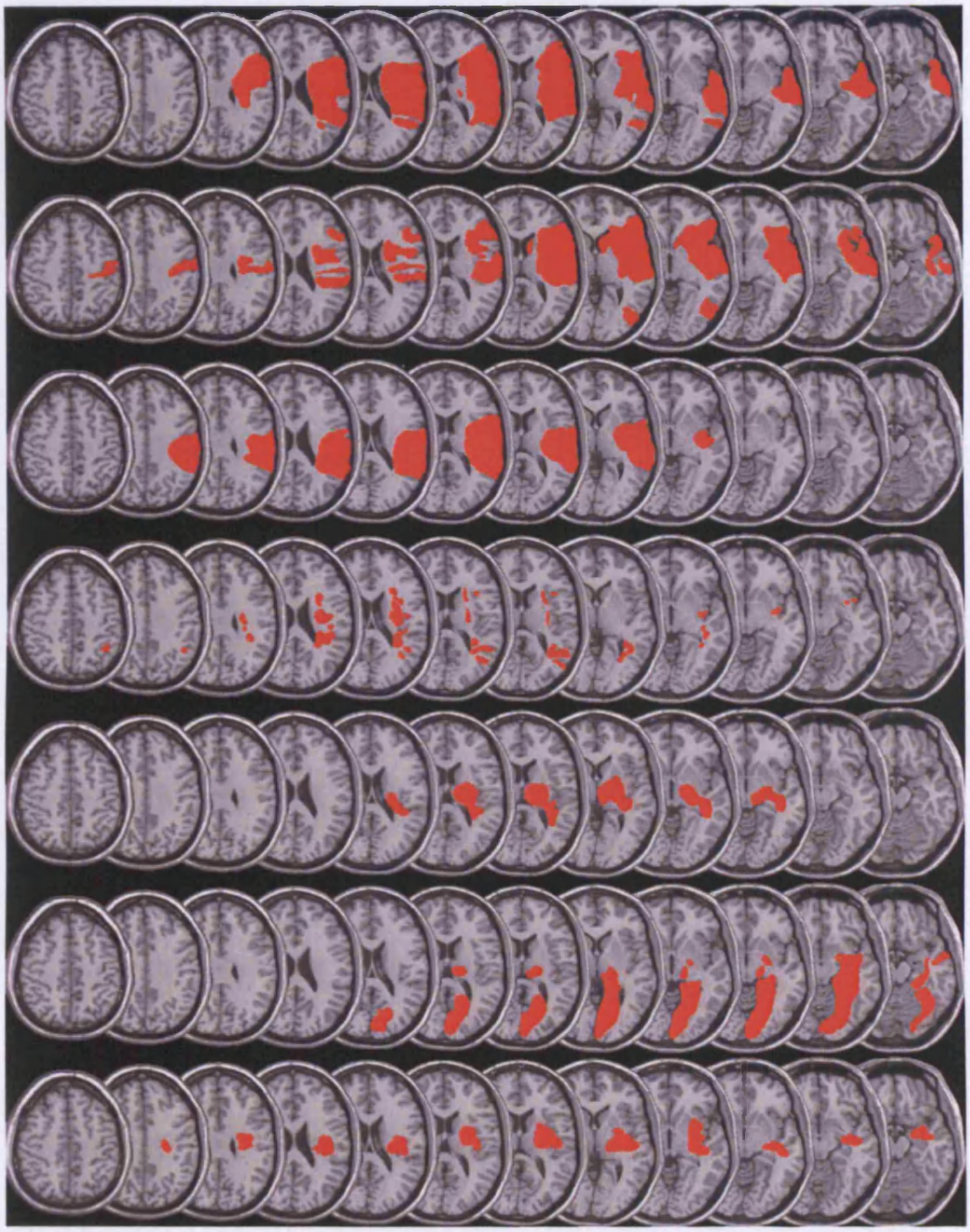
A2.4.2 Non-motor neglect patients

A2.1 Lesions for chapter 3

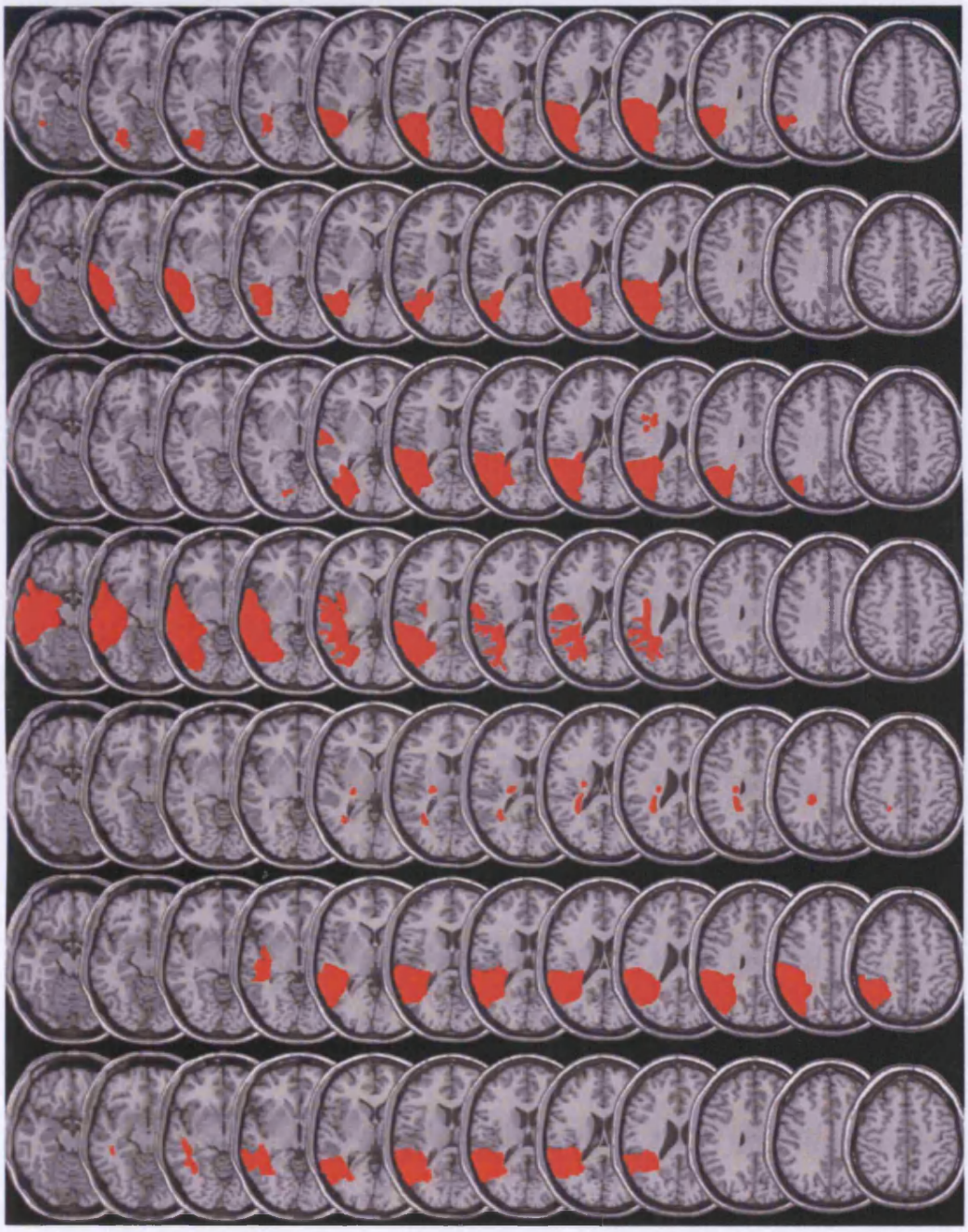
A2.1.1 PPC neglect patients



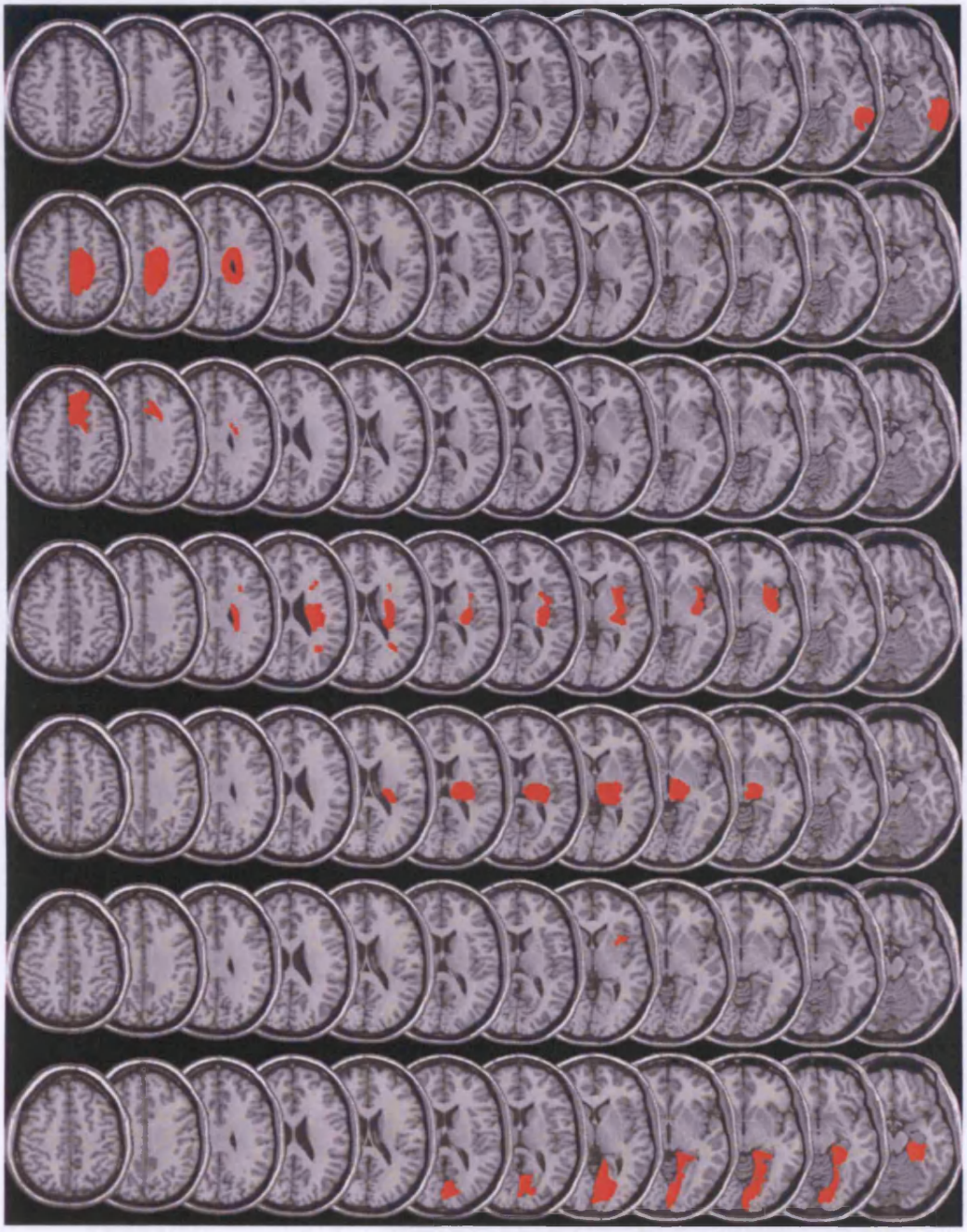
A2.1.2 Non-PPC neglect patients



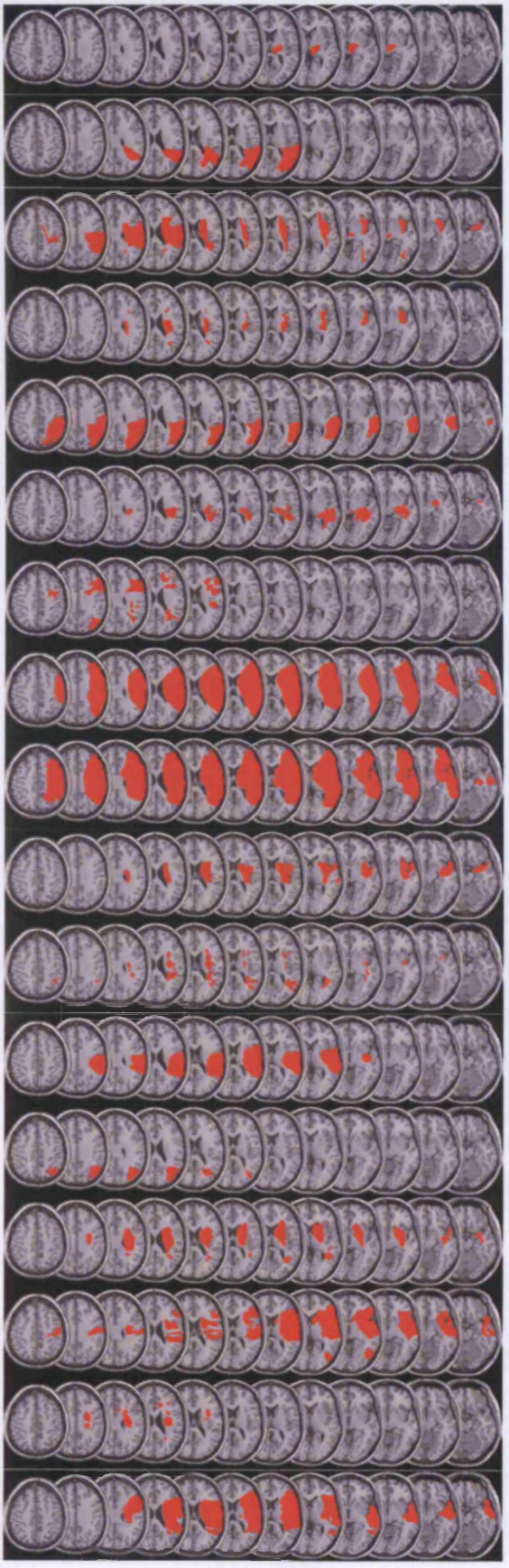
A2.1.3 Left hemisphere patients



A2.1.4 Non-neglect patients

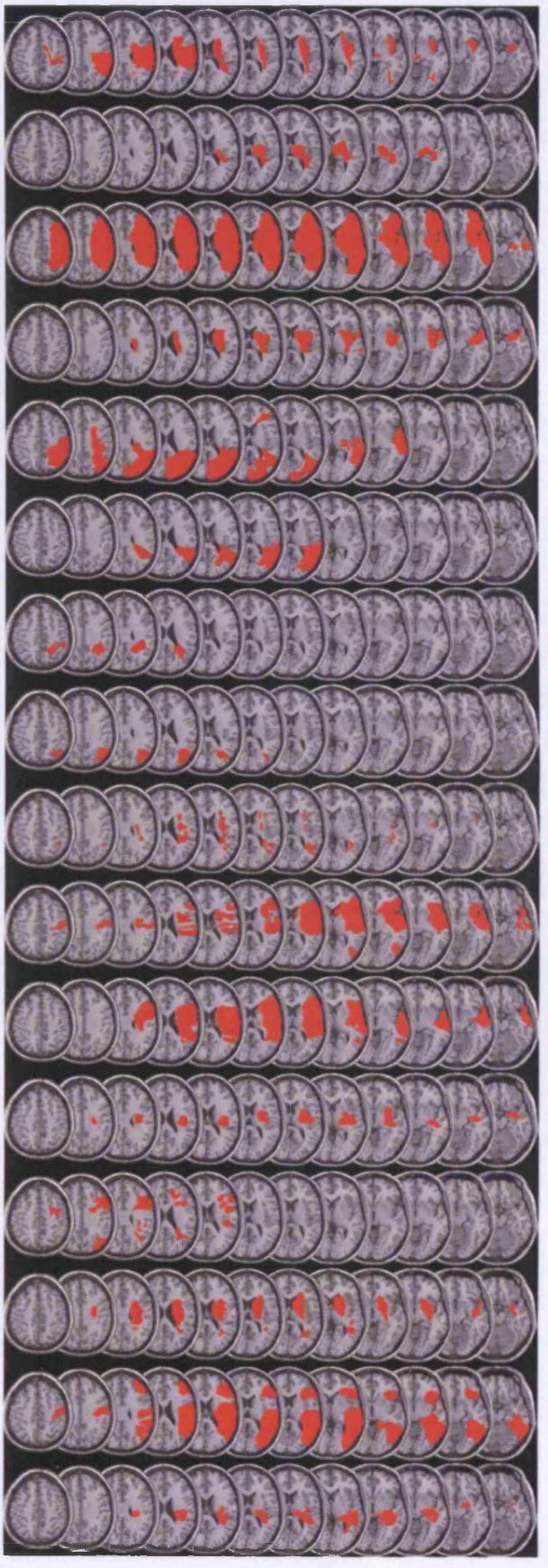


A2.2 Chapter 4 all patients

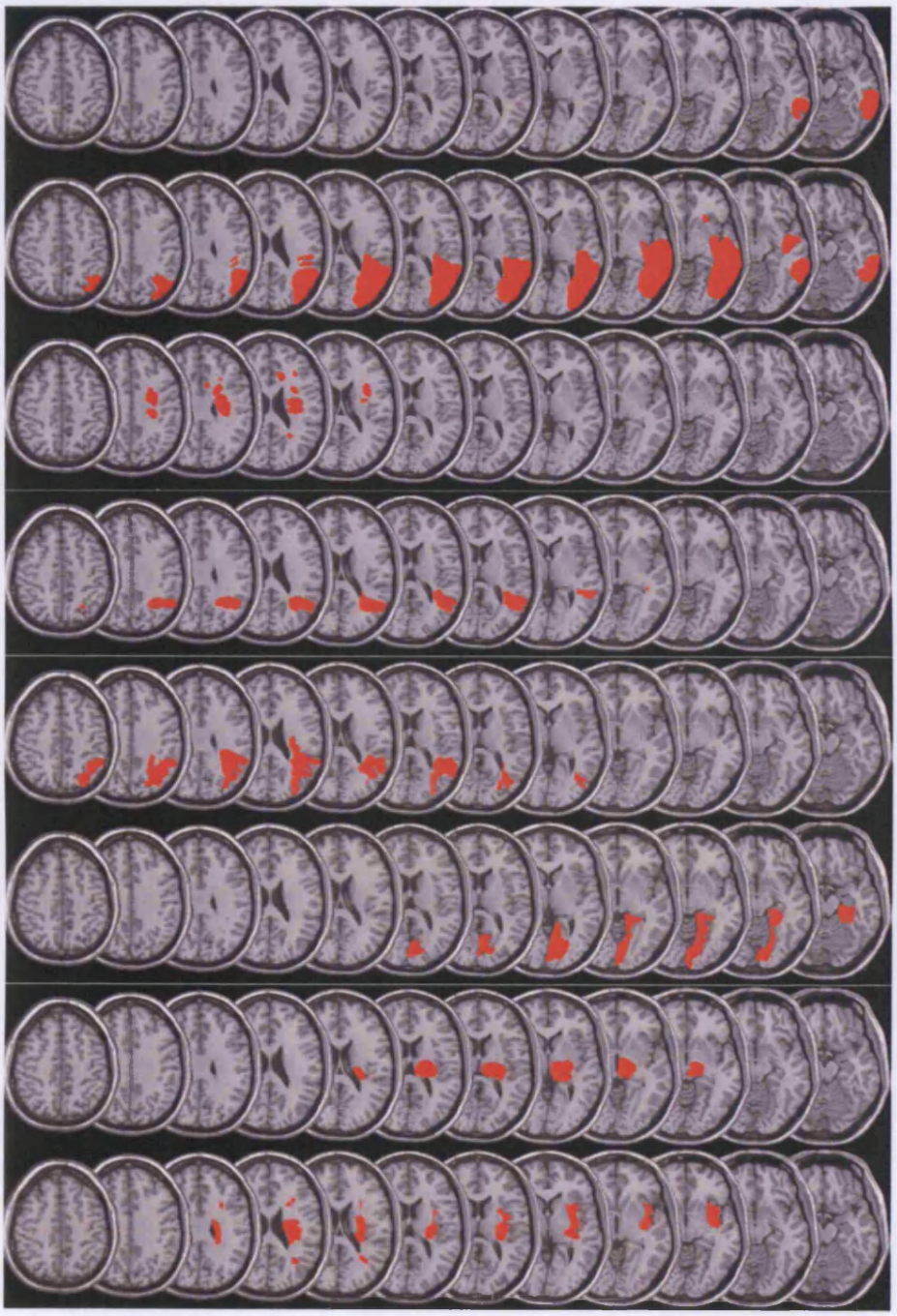


A2.3 Chapter 5

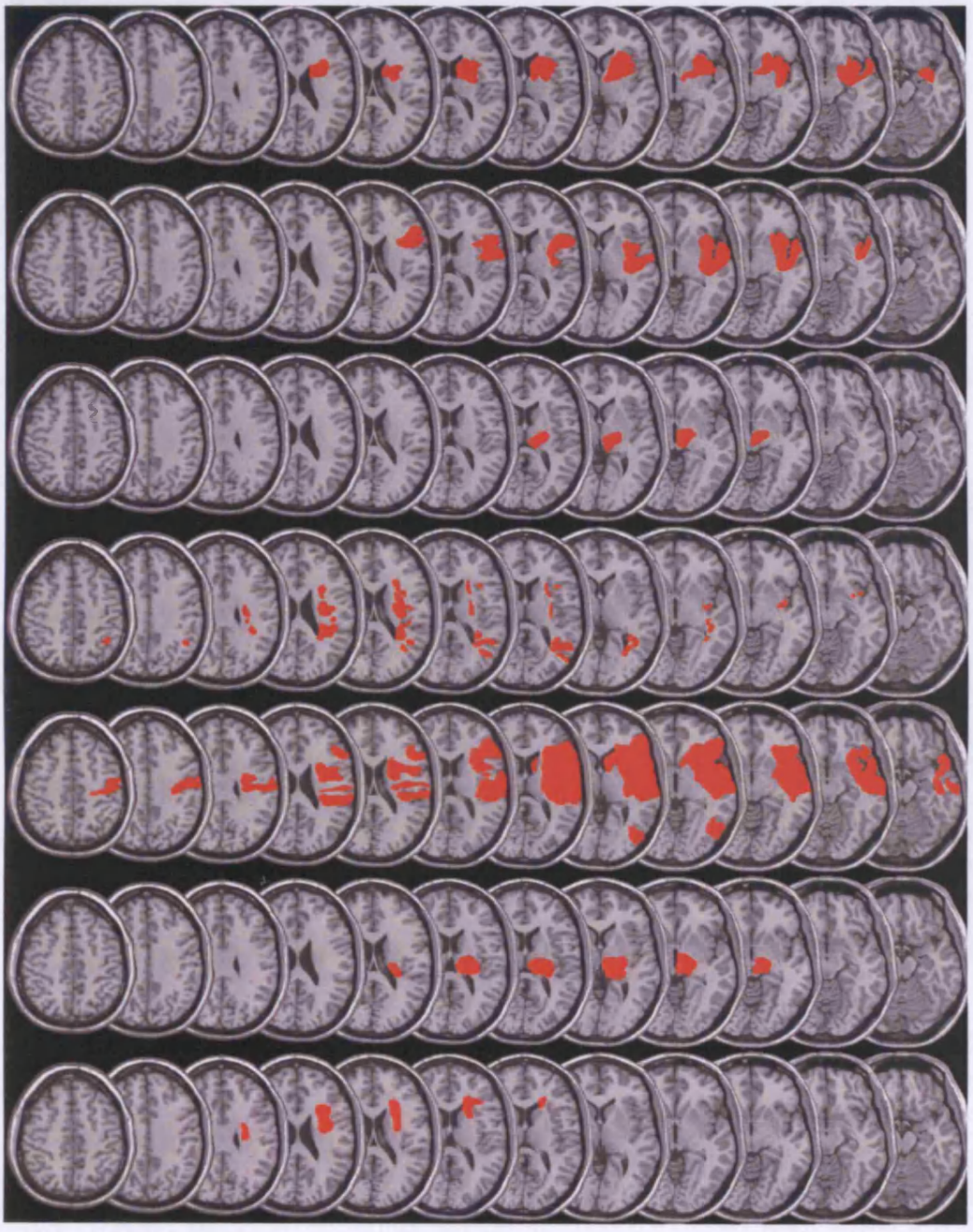
A2.3.1 Neglect patients



A2.3.2Non-neglect patients



A2.4 Chapter 7
A2.4.1 motor neglect patients



A2.4.2 Non-motor neglect patients